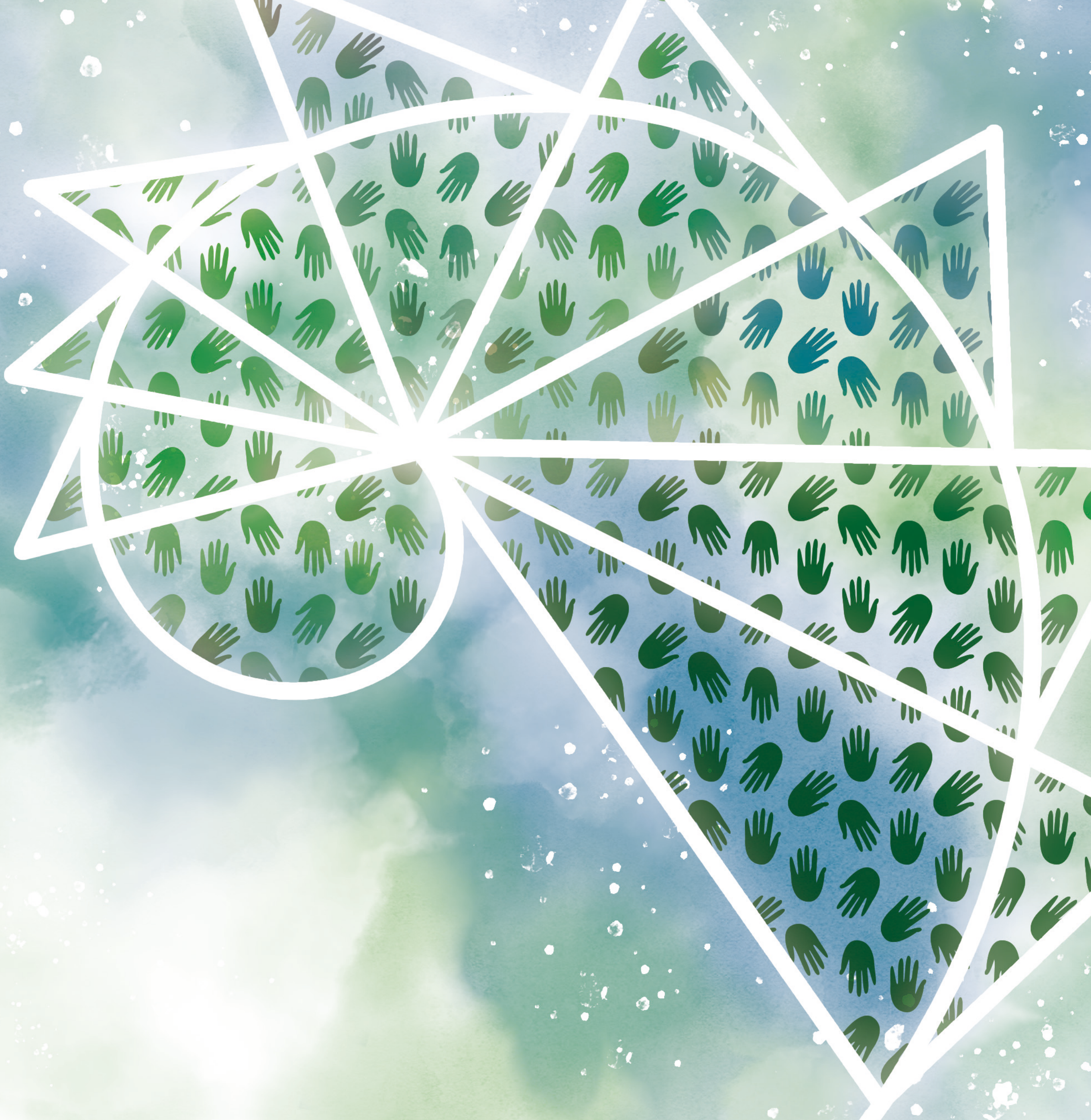

PERSPECTIVES ON OUTCOME FOLLOWING HAND AND WRIST INJURY

IN NON-OSTEOPOROTIC PATIENTS

CHARLOTTE M. LAMEIJER

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CHAPTER 1

Introduction and outline

INTRODUCTION

About 20% of all visits to the surgical emergency department are due to hand and wrist injuries [1]. Distal radius fractures (DRFs) are a major portion of these injuries, with annual incidences reported of 9/10,000 men and 37/10,000 women in patients aged 35 years and older [2,3]. DRFs have a bimodal division in incidence, with peak incidences in young (predominantly male) and older (predominantly female) patients [4,5]. Carpal injuries are less common and perilunate (fracture) dislocations (PLD/PLFDs) comprise of only 7% of all carpal injuries [6-10]. Both injuries are mainly the result of high-energy trauma in the younger population [5,11,12]. Following a (high energy) fall on the outstretched hand (FOOSH) in hyperextension- or flexion a DRF can occur with respectively dorsal or volar dislocation with or without intraarticular involvement and possible concomitant ligamentous injury (Figure 1) [13-17]. With the same trauma mechanism as FOOSH a cascade of ligamentous and osseous injuries can occur in the carpals as described by Mayfield *et al.* [18,19]. The first stage comprises of a dorsal subluxation of the scaphoid resulting in dorsal scapholunate (SL) ligamentous injury (or scaphoid fracture), which is the strongest part of the SL ligament. In the second stage, a PLD/PLFD occurs when the capitate luxates most often dorsally in respect to the lunate (Figure 2) [18,19].

Outcomes following hand and wrist injuries can be depicted using three different modalities; radiological outcomes such as presence of posttraumatic arthritis or restoration of articular congruency and alignment of the wrist, clinician reported outcomes (CROs) measuring range of motion and grip strength, and finally patient reported outcomes (PROs) using questionnaires to capture subjective outcome as perceived by patients. Most literature on outcomes following DRFs is dedicated to the elderly, since DRF incidence figures are higher in the older population [1,2,5]. However, the relevance of reporting on outcomes in younger patients sustaining hand or wrist injuries seems to be neglected. Evaluating outcomes in young non-osteoporotic patients is of importance since they have a long and active life ahead of them and consequently they might have higher demands of hand and wrist function. Better insight in these outcomes could guide future treatment and rehabilitation strategies for these young and active patients. This thesis contributes to filling the gap of knowledge on outcomes following hand and wrist injuries in non-osteoporotic patients.

Radiological outcome

Posttraumatic arthritis. The development of posttraumatic arthritis (PA) following DRFs is well known [15,21-24]. Knirk and Jupiter described a classification system for radiocarpal PA in 1986, which is still widely used (Table 1) [24]. Prevalence of radiological PA is reported to be as high as 56-65% after 6-7 years of follow up for hand and wrist injuries like DRFs and PLD/PLFDs in heterogenous patient cohorts [12,24].

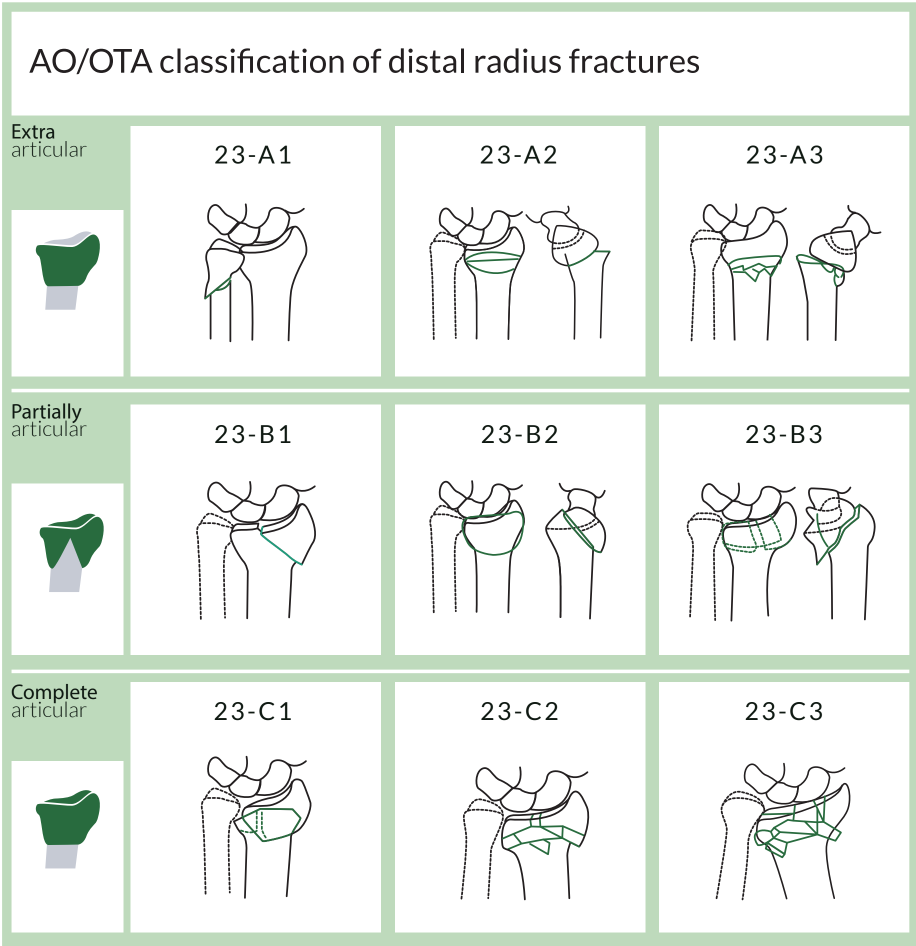

Figure 1. Distal radius fracture classification according to the AO foundation and Orthopaedic Trauma Association [20]

Table 1. Grading of posttraumatic arthritis according to Knirk & Jupiter [24]

Grade	Radiological findings
0	None
I	Slight joint-space narrowing
II	Marked joint-space narrowing, osteophyte formation
III	Bone-on-bone, osteophyte formation, cyst formation

Stages of carpal instability

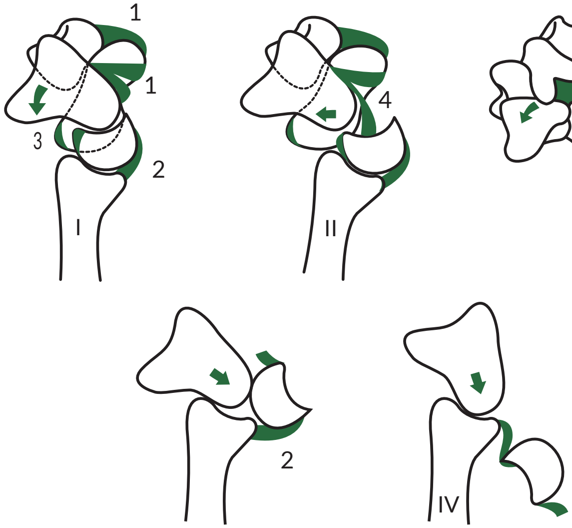

Figure 2. Stages of carpal instability according to Mayfield *et al.* [18,19]
Stage I: Scapholunate dissociation with subluxation of the scaphoid and scapholunate ligament injury. This can be recognized on radiographic imaging as a gap between the scaphoid and lunate ('Terry Thomas sign'). Stage II: Perilunate luxation with or without scaphoid fracture (perilunate fracture dislocation), luxation of the capitate (mostly in dorsal direction). Stage III: Midcarpal dislocation with luxation of capitate and triquetrum (or with lunotriquetral ligamentous injury or triquetral fracture). This can be recognized on radiographic imaging as an avulsion fracture of the triquetrum. Stage IV: Luxation of the lunate (mostly to the volar side) with dorsal radiolunate ligament rupture. This can be recognized on radiographic imaging as the 'spilled teacup sign'.

Since DRFs in young non-osteoporotic patients usually result from high energy trauma, these injuries often have intra-articular involvement [25]. This can result in residual articular incongruence, which is usually described in gaps and step-offs [15-17,26-28]. Many studies have shown that DRFs healed with articular incongruency > 2mm are associated with early PA [15,21-23]. On the basis of the type of tissue damage, articular surface injuries can be classified into three types: (1) damage to the cells and matrices of articular cartilage and subchondral bone not related to detectable disruption of the joint surface, (2) visible mechanical disruption of articular cartilage only in the form of chondral fissures, flap tears or chondral defects, and (3) visible mechanical disruption of articular cartilage and bone associated with intraarticular fractures [29,30]. Each type of tissue damage stimulates a different repair response and has a different prognosis. In clinical practice, type-2 and -3 injuries have associated type-1 injuries. Type-3 injuries cause haemorrhage and fibrin clot formation and activates an inflammatory response [31]. Platelets release vasoactive mediators, cytokines and platelet-derived growth factors, stimulating angiogenesis and migration of undifferentiated mesenchymal cells into the clot, which begin to form a new matrix. As a result, the repair and remodelling of intraarticular fractures differ between injuries that cause only cell and matrix injury or disruption of the articular surface limited to articular surface. For these reasons, intraarticular fractures include all three types of articular surface injury [32]. The degree of articular incongruency reflected in gaps and/or step-offs between fracture fragments influence the extent and outcome of repair. In addition, remodelling responses leading to clinically evident joint instability and/or malalignment will decrease the cartilage repair potential. This forms an ongoing vicious cycle [32]. Concluding; development of radiological posstraumatic arthritis (PA) is associated with direct or indirect impact loading on the joint, soft tissue contusion, joint dislocation and intra-articular fractures, because these factors increase the risk of progressive joint degeneration [29,30,32].

In addition to articular incongruency, age appears to be one of the most substantial risk factors for the development of PA [32]. Basic scientific investigations have shown that articular chondrocytes have profound age-related changes in the ability to respond to anabolic stimuli [33,34]. In addition, clinical studies have also supported the hypothesis that age is an important risk factor. Patients over 50 years of age have a 2-4 fold greater risk for development of PA following intraarticular fractures of the knee [35]. Several genes, inluding IL-6-encoding pro-inflammatory cytokines are involved in the development of osteoporosis and PA. Associations between radiological PA of the wrist and osteoporisis related phenotypes with polymorphism in IL-6 have been reported [36]. This suggests an association between preexistent osteoporosis and PA, possibly influencing outcome differently in patients of different ages. Literature reporting on outcome following DRFs mainly report on cohorts with wide age variations or cohorts with mainly older patients, in which preexistent osteoporosis and/or PA might significantly impact outcome. To gain insight in the impact of PA without these confounding factors in a young and active population, this thesis aims at reporting on non-osteoporotic patients following hand and wrist injuries.

Radiological measurements. Normal anatomical parameters regarding the distal radius have been described in literature; normal values for radiocarpal joint surface tilt (dorsal angulation) vary from 0° to palmar 22° [37,38], radial inclination ranges from 16° to 29° [39,40], radial length normally varies between 8 and 17mm [41], and ulnar variance ranges from minus 4 to plus 2mm [40,42] (Figure 3). Recent literature puts these measurements in perspective reporting on questionable intra- and interrelated reliability and considerable error magnitudes of radiological measurements following DRFs [43]. Error magnitude of residual gaps and/or step-offs has been reported to be within 1-2mm [43]. As intra- and interobserver reliability of measuring residual gaps and step-offs were reported to be moderate to poor, it has been questioned whether these radiographic measurements should be used as criteria for guiding treatment [43,44]. Intercarpal ligamentous injuries of the scapholunate joint and distal radio-ulnar joint (DRUJ) instability are also associated with DRFs and might influence outcome [14,25,45]. Normal scapholunate distance (SL distance) has been reported to be within 2mm [46]. DRUJ distance should be assessed in comparison to a PA radiograph of the uninjured wrist (<2mm difference) or a difference of at least 4-5mm between both dorsal cortices on a lateral radiograph should be present (Figure 3) [47,48].

Restoration of articular congruency and alignment are described to be the key principles of management of DRFs, because lacking to fulfill these principles can lead to joint stiffness and long-term morbidity [22,32]. In literature, several decisive criteria for the reduction of wrist fractures are presented [49-51]. However, in most of these studies there is a heterogeneity of injuries, small numbers of patients with wide age ranges as well as underscoring of concomitant ligamentous injuries and different methods of assessment [32]. The role of radiological measurements on treatment and outcome following DRFs in young non-osteoporotic patients is unclear and needs further attention.

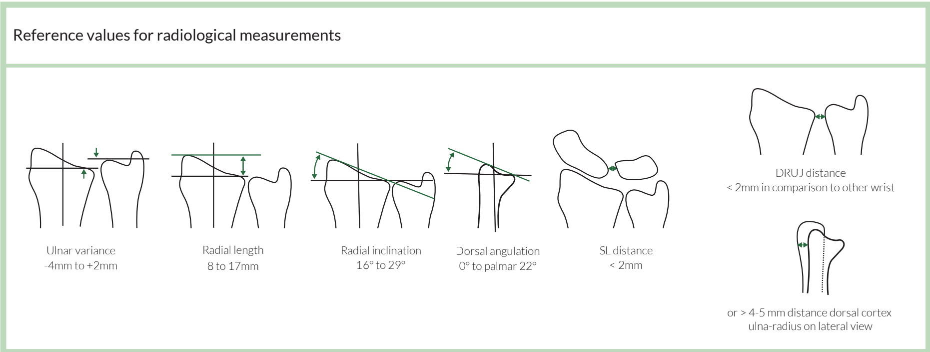

Figure 3. Radiological measurements regarding distal radius fractures

Clinician reported outcomes

Range of motion. Wrist motion is dependent on complex articulations of the distal radius, distal ulna and proximal carpal row of which the scaphoid and lunate are most important [52]. Biomechanically, flexion-extension and radio-ulnar deviation are a result of motion of the scaphoid and lunate in respect to the distal radius, which relies on the ligamentous stability between these two carpal bones and movement in the adjacent joint surfaces [53]. Damage to the radiocarpal joint and/or associated ligamentous injuries are reported to possibly influence range of motion [54]. Furthermore, malalignment of the distal radius following a fracture can cause alterations of the DRUJ with anatomical change of the contact area, resulting in limited pronation and supination [55]. Unfortunately, due to the inhomogeneity of patient cohorts reported in literature, it remains unclear how range of motion is diminished in non-osteoporotic patients. In addition, little is known regarding the association between PA and range of motion and what can be expected of range of motion measurements at follow up after DRFs or PLD/PLFDs in such a patient cohort.

Grip strength. Ageing is typically associated with a progressive loss of skeletal muscle mass and occurs at a rate of 3-8% each decade after the age of 30 years [56,57]. In general, grip strength of the upper extremity is reported to be a reflection of overall muscle strength and physical condition [58]. One might hypothesize that isolated hand and wrist injuries therefore do not result in diminished grip strength. On the contrary, the injury and the temporary associated diminished use of the entire extremity might influence grip strength. Some studies do report diminished grip strength measures following upper extremity injury in heterogenous cohorts with wide age variations [50,59]. It remains unclear if grip strength is diminished in non-osteoporotic patients following hand and wrist injury.

Patient reported outcomes

In the last two decades, outcome assesment has shifted towards a patient-centred approach. Patient reported outcomes (PROs) assess outcome as experienced by the patient. A variety of PROs are available for upper extremity injuries. Commonly used PROs in literature regarding upper extremity injuries are the Disability of Arm, Shoulder and Hand questionnaire (DASH), Patient Reported Wrist Evaluation (PRWE) and to a lesser extent the Michigan Hand Questionnaire (MHQ). These questionnaires focus on domains that are most relevant to patients who have experienced hand and wrist injuries or disorders; the patients own perception of recovery and pain, and the ability to return to activities of daily life including high-demanding activities, such as sports [60,61]. In addition to upper extremity-specific questionnaires, more generic instruments that capture health status and quality of life, such as the Short Form-36 (SF-36) may be useful to place upper extremity injury into a broader context and identify their influence on everyday life [62]. Since results of many studies are incomparable due to the application of different outcome measures, Waljee *et al.* and Goldhahn proposed a systematic approach to reporting outcome following DRFs in literature, including validated questionnaires [63,64]. However, no single PRO has emerged as superior [63]. A recent systematic review described good responsiveness of the DASH and PRWE following DRFs, however, the articles included in this review were of moderate quality [65], and there was limited evidence for reliability and validity [65]. Quality criteria have been set for the validation of PROs that should be applied to interpret these tools in a reliable way [66]. For example, confirmatory factor analysis has been performed for testing construct validity of the Dutch translation of the PRWE (PRWE-NL) [67]. This analysis has investigated the construct that the instrument measures which revealed that the PRWE-NL measures one construct, while it was designed to measure two. Most studies reporting on PROs following hand and wrist injuries describe cohorts with wide age variation. The young non-osteoporotic patient might have a higher demand of the function of his/her hand or wrist. Therefore, we hypothesize PROs following DRFs or PLD/PLFDs might be affected differently in this population than in the older population. The question arises what the association between DRFs and/or PLD/PLFDs is and several PROs. In addition, the influence of PA, radiological measurements and CROs on PROs in this young patient population remains unclear.

A solution to the interpretation of the wide variety of PROs could be the recently developed Patient-Reported Outcomes Measurement Information System (PROMIS®). This set of measures was developed by the National Institute of Health as an integrated collection of instruments designed to capture self-reported health status across 3 broad domains: physical, mental and social [68,69]. Each individual instrument consists of an 'item bank', or a group of questions that aims to measure a specific aspect of health-related quality of life. These can be administered as short forms or computerized adaptive tests (CAT) [69,70]. CAT uses an algorithm that selects the most informative items from the item bank, based on the individual's response to previously administered items. In this way, high measurement precision can be obtained with low respondent burden. PROMIS item banks, such as PROMIS physical function, pain interference and upper-extremity function, have been studied for use among patients with upper-extremity conditions. These may reduce the burden placed on patients while maintaining or improving measurement properties, because computerized adaptive versions of PROMIS typically have fewer items and less floor and ceiling effects. Untill now, the PROMIS physical function - upper extremity v2.0 (PROMIS-UE v2.0) item bank has not been translated to the Dutch language nor has been validated in patients with upper extremity injuries.

Clinical relevance

For the clinician it is important to be able to extrapolate reported outcomes following hand and wrist injuries from literature to everyday clinical practice. Therefore, reporting on error magnitudes regarding radiological measurement and clinical relevant changes regarding CROs and PROs is mandatory. Recent literature puts normal radiological measurements following DRFs in perspective reporting on questionable intra- and interrater reliability and considerable error magnitudes of radiological measurements following DRFs [43]. In addition, when reporting on CROs and PROs following hand and wrist injury, most literature reports on 'smallest detectable change' (SDC) when reporting on outcomes following DRFs. SDC is a statistical measurement and does not take into account changes as experienced by patients. Clinically more relevant is the 'minimal important change' (MIC), which is the smallest change in an outcome measurement that a patient would perceive as important [71-74]. MICs following DRFs have been reported scarcely on CROs [75,76] and PROs [77-79].

Aims

The *general objective* of this thesis is to gain insight in radiological measurements, CROs and PROs following hand and wrist injuries in non-osteoporotic patients. We aim to report on the prevalence of PA in these young non-osteoporotic patients and gain insight in the association between radiological measures, CROs and PROs. In addition, we aim to put these outcome measures in perspective by reporting on their clinical relevance.

OUTLINE OF THIS THESIS

These aims are explored in different studies. **Part 1** of this thesis (Chapters 2 to 5) focuses on hand and wrist injuries in non-osteoporotic patients, and reports on outcome measures and their associations. In addition, clinical relevance of outcome measures is presented. **Part 2** of this thesis (Chapters 6 to 8) focuses on PROs following upper extremity injuries. The Dutch version of the DASH (DASH-DLV) is validated. In addition, validation of the Dutch-Flemish translation of the PROMIS-UE v2.0 item bank (DF-PROMIS-UE v2.0) has been performed.

In **Chapter 2** we aim to provide an overview of the literature regarding the association between PA and outcome measures in non-osteoporotic patients following DRFs.

The objective of **Chapter 3** is presenting on the prevalence of PA and its associations with CROs and PROs measured in a cohort of non-osteoporotic patients following DRFs.

The purpose of **Chapter 4** is providing insight in the evolution of radiological measurements over time following DRFs and their association with CROs and PROs in non-osteoporotic patients. In addition, we aim to report on the clinical relevance of the outcome measures.

Chapter 5 is aimed at providing an overview of the severity of CROs and PROs following PLD/PLFDs by comparing these outcomes to those of matched healthy controls.

The goal of **Chapter 6** is validation of the DASH-DLV in patients with hand and wrist injuries using comfirmatory factor analysis.

Chapter 7 is directed at describing the structural validity and construct validity for the Dutch-Flemish translation of the PROMIS UE v2.0 item bank.

In **Chapter 8** we aim to provide the validation of the Dutch-Flemish translation PROMIS UE v2.0 item bank using Item Response Theory, after which Computer Adaptive Tests can be performed with this PRO.

Chapter 9 comprises the discussion and future perspectives of this thesis.

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PART 1

Associations between radiological measurements, clinician and patient reported outcomes

CHAPTER 2

Prevalence of posttraumatic arthritis and the association with outcome measures following distal radius fractures in non-osteoporotic patients. A systematic review

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ABSTRACT

Introduction. The objective of this systematic review was to analyze 1) prevalence of radiological posttraumatic arthritis, 2) associations of posttraumatic arthritis with outcome measures and 3) predictors of posttraumatic arthritis following distal radius fractures in non-osteoporotic patients.

Materials and Methods. Nineteen studies were included (10 open source data).

Results. In total, 733 patients were described with a weighted mean age of 37 years (range 25-54) at the time of the injury. Follow-up ranged from 13 months- 38 years. Overall prevalence of posttraumatic arthritis was 50% and 37% in the open source data. Radial deviation was significantly worse in patients with PA (N=49, mean 14°, SD 6° versus N=55, mean 17°, SD 6°, p=.037). No analysis could be performed regarding patient reported outcome (PRO) measures, because of limited data. Articular incongruence was a significant predictor for posttraumatic arthritis.

Conclusions. A high prevalence of PA was found in non-osteoporotic patients following a DRF. PA following a distal radial fracture was associated with a limited radial deviation and flexion, but not with grip strength. Articular incongruence predicted PA. PROs should be investigated more thoroughly to be able to understand the value of using these instruments in interpreting outcome in follow up of non-osteoporotic patients following a DRF. Level of evidence 3 [1].

INTRODUCTION

Distal radius fractures (DRFs) are common injuries. An annual incidence of 9/10,000 men and 37/10,000 women has been reported in patients aged 35 years and older [2,3]. In a sample of more than 87 million Americans with an upper extremity fracture in 2009, the most common fracture sites were the distal radius and ulna [4]. The incidence of DRFs is bimodal, with peak incidences in young (predominantly male) patients and older (predominantly females) patients [4,5]. In young adults this type of fracture results from a high-energy trauma. In older adults, the fracture more often results from low-energy trauma [5,6]. It has been estimated that at 50 years of age, a woman has 16.6% remaining lifetime risk of sustaining a DRF, whereas a man has a remaining lifetime risk of just 2.9% [7]. Prevalence of radiological posttraumatic arthritis (PA) following DRFs has been described to be as high as 65% after 6.7 years of follow up [8]. A recent systematic review describing the development of PA suggests that presence of articular steps at the time of healing results in a higher prevalence of radiographic signs of PA [9]. However, the association between radiological PA and clinical outcome remains unclear. Many studies have shown that fractures healed with a step > 2 mm are associated with early PA [10-13]. The association between articular incongruence and PA dictates common held beliefs in treatment of DRFs, where anatomical reduction of the articular surface and stable internal fixation are pursued.

Recent literature supports the hypothesis that increasing age is also an important risk factor for the development of PA [9]. PA is thought to develop less in younger patients. However, it might be of greater importance for this younger age group, because these patients have a long active working and sporting life ahead of them.

Clinician reported outcome

Function following a DRF can be captured using clinician reported outcomes (CROs), such as range of motion (ROM) and grip strength. PA following a DRF was associated with poorer CROs in some studies [11,14,15]. However, other studies did not find this association [16,17].

Patient reported outcome

The patient's opinion regarding wrist function, pain or satisfaction following a DRF can be captured in patient reported outcomes (PROs). A number of studies did not find a significant association between PA and PROs [10,18,19]. In contrast, recent literature reported a significant association between presence of PA following DRF and poorer outcomes reported on the SF-36 questionnaire in a heterogeneous age group [20,21]. Two studies described that a higher age predicted worse PROs 1 to 6 years following a DRF [20,22]. The Physical Component Scale (PCS) of the SF-36 was poorer in older patients. The Mental Component Scale (MCS) of the

SF-36 was similar or even better in younger patients [20,21,23]. It has been suggested that patients with pre-existing osteoporosis following a DRF have better scores on PROs than those without osteoporosis [21,24]. Age and/or preexisting osteoporosis seem to be independent factors influencing PROs following a DRF.

Purpose of the study

Conflicting results in literature have been presented on the association between outcomes and PA following DRFs. There is a need for better understanding of the clinical relevance of radiological PA following a DRF in non-osteoporotic patients. Determination of specific outcome measures predicting PA could be helpful in guiding individual treatment strategies and to decide what rehabilitation goals should be pursued in the follow-up of these patients. Also, such outcomes could be used to prepare patients on the expected return of function and possible necessary adjustments in everyday life.

The objectives of this systematic review were to analyze 1) the prevalence of PA following a DRF, 2) associations of PA with CROs and PROs and 3) predictors of PA following a DRF in non-osteoporotic patients.

METHODS

Literature search

A systematic search of the literature was performed in PubMed, Embase, the Cochrane Library and PsycINFO without time restrictions, published until January 2015. The databases were searched with a combination of MesH terms regarding PA, CROs and PROs (Table 1).

Eligible for this review were studies reporting adult patients, women between 18-49 years and men between 18-59 years at the time of sustaining a DRF. These age selection criteria were applied to eliminate the risk op preexistent, because of the high prevalence of osteoporosis reported in literature in older patients, especially in postmenopausal women [25,26]. Furthermore, at least one of the CROs (ROM, grip strength) or PROs (Disability of Arm, Shoulder and Hand questionnaire (DASH), Patient Rated Wrist Evaluation (PRWE), Michigan Hand Questionnaire (MHQ), Short Form-36 (SF-36)) had to be described. Follow-up duration had to be at least one year after the DRF. All study designs were included. Excluded were studies with less than 5 patients and studies reporting outcome measures that integrate CROs and PROs, such as the Gartland and Werley score or the Green and O'Brien score, since separate relations of CROs or PROs with PA cannot be established from such measures [21,27]. Studies describing open fractures were also excluded. Last, studies written in languages other than English, German or Dutch were excluded and articles that only comprised of a supplement or abstract for a congress.

Quality assessment

The methodological quality of the selected studies was assessed using the Newcastle-Ottawa Scale (NOS), which is initiated to evaluate the quality of non-randomized studies, such as case-control and cohort studies (Table 2) [28]. The content validity of the NOS has been established based on a critical review of the items by several experts in the field who evaluated its efficiency for assessing the quality of studies to be used in a meta-analysis [28]. With a maximum score of 9, studies were assigned 1 point for each criterion in the checklist that was met, with the exception that 2 points can be assigned in the comparability scale (Table 2) [28]. Studies scoring 75% or more of the maximum score (i.e. > 6 points) were considered to be of 'high quality'. Studies scoring between 50-75% (i.e. 5 or 6 points) were labeled 'moderate quality'. 'Low quality' was given to studies with scores lower than 50% (i.e. < 5 points). Two reviewers scored the quality (TD, CL), difference in scoring between the two reviewers was resolved with discussion and in case of persistent disagreement a third reviewer (CS) was consulted to reach consensus.

Table 1. Search strategy in Pubmed

Radius fractures	("Radius Fractures"[Mesh] OR Radius Fracture*[tiab] OR ("Radius"[Mesh] AND "Fractures, Bone"[Mesh]))
Post-traumatic or osteoarthritis	(post traumatic*[tiab] OR posttraumatic*[tiab] OR arthros*[tiab] OR arthrit*[tiab] OR "Joint Diseases"[Mesh] OR osteoarthrit*[tiab])
Functional outcome or Patient Reported Outcome or Health Status	("Questionnaires"[Mesh] OR Questionnaire*[tiab] OR short form 36[tiab] OR dash[tiab] OR sf 36[tiab] OR (arm[tiab] AND shoulder[tiab] AND hand[tiab]) OR prwe[tiab] OR patient rated wrist evaluation[tiab] OR mhq[tiab] OR (michigan[tiab] AND hand[tiab] AND outcome*[tiab]) OR "Patient Satisfaction"[Mesh] OR "Patient Satisfaction"[tiab] OR "Pain"[Mesh] OR "Pain"[tiab] OR "Disability Evaluation"[Mesh] OR disabilit*[tiab] OR "Quality of Life"[Mesh] OR qol[tiab] OR "Quality of Life"[tiab] OR life qualit*[tiab] OR range of motion[tiab] OR "Range of Motion, Articular"[Mesh] OR "Recovery of function"[Mesh] OR convalescen*[tiab] OR grip strength[tiab] OR health status[tiab] OR "health status"[Mesh] OR "Health Status Indicators"[Mesh])

Reproduction of the search strategy can be achieved through combining the different sets with the boolean operator AND. The search terms in Embase, the Cochrane Library and PsychInfo were derived from the search terms used in PubMed and are available on request from the author.

Table 2. Newcastle-Ottawa Scale

Category	Item #	Newcastle-Ottawa Quality Assesment Scale – Cohort Studies Note: a study can be awarded a maximum of one point for each numbered item within the Selection and Outcome categories. A maximum of 2 points can be given for Comparability	Points
SELECTION	1	Representativeness of the exposed cohort	
		a. truly representative of the average non-osteoporotic patient with a distal radius fracture in the community (1 pt)	1
		b. somewhat representative of the average non-osteoporotic patient with a distal radius fracture in the community (1 pt)	1
		c. Selected group of users, e.g. nurses or volunteers	0
		d. No description of the derivation of the cohort	0
	2	Selection of the non-exposed cohort	
		a. drawn from the same community as the exposed cohort	1
		b. drawn from a different source	0
		c. no description of the derivation of the non-exposed cohort	0
	3	Ascertainment of exposure	
		a. secure record (e.g. surgical records)	1
		b. structured interview	1
		c. written self-report	0
		d. no description	0

Table 2. Continued

Category	Item #	Newcastle-Ottawa Quality Assesment Scale – Cohort Studies Note: a study can be awarded a maximum of one point for each numbered item within the Selection and Outcome categories. A maximum of 2 points can be given for Comparability	Points
	4	Demonstration that outcome of interest was not present at start	
		of study	1
		a. yes	0
		b. no	
COMPARABILITY	5	Comparability of cohorts on the basis of the design or analysis	
		a. study controls for posttraumatic arthritis following a distal	1
		radius fracture	1
		b. study controls for any additional factor (this criteria could be modified to indicate control for a second important factor)	
OUTCOME	6	Assessment of outcome	
		a. independent blind assessment	1
		b. record linkage	1
		c. self-report	0
		d. no description	0
	7	Was follow-up long enough for outcomes to occur	
		a. yes (adequate follow up for posttraumatic arthritis to occur: at	1
		least 2 years)	0
		b. no	
	8	Adequacy of follow-up of cohorts	
		a. complete follow-up – all subjects for at least 12 months	1
		b. subjects lost to follow up unlikely to introduce bias – small	1
		number lost < 10%	0
		c. follow-up rate > 10% and no description of those lost	0
		d. no statement	
Total			**9**

Posttraumatic arthritis assessment

In all studies the classification for PA according to Knirk & Jupiter was applied; grade 0 represents no signs of PA and grade 3 representing bone-on-bone PA with osteophyte and cyst formation [8]. In order to exclude any chance of bias regarding the severity of PA as graded in the different studies, PA was computed as a dichotomous value; presence or no presence of PA.

Clinician reported outcome

Range of motion was expressed in degrees. To minimize the effect of the different units of measurement of grip strength (kilograms, kilopascal or pounds), grip strength of the injured wrist as a percentage of the uninjured wrist was calculated. No correction for dominance of hand was performed, in concordance with other studies [14,29,30].

Patient reported outcome

DASH. The Disability of Arm Shoulder Hand questionnaire is a 30-item self-report measure focusing on physical functioning and symptoms of the upper limb. DASH scores range from 0 to 100 (higher scores indicate worse function).

PRWE. The Patient Rated Wrist Evaluation assesses pain and functioning in patients with wrist fractures [54]. The PRWE includes 5 items assessing pain, which are rated from 0 (no pain) to 10 (unbearable pain) and 10 items assessing function [36]. The function subscale is divided into two sections concerning specific activities and usual activities. For each section the maximum score is 50 (most disability) and the minimum score is 0 (no disability). A higher score indicates a worse outcome. The questionnaire has a fair validity for symptoms and function of the wrist.

MHQ. The Michigan Hand Outcomes Questionnaire is a validated questionnaire assessing hand outcomes that are of importance to patients and specific for the impaired hand (left and right separately). It includes 6 domains (overall hand function, activities of daily living, pain, work performance, aesthetics and satisfaction). A higher score indicates a better function of the impaired wrist [55].

SF-36. The Short Form-36 questionnaire is developed to survey overall health status [56]. It uses 36 items to asses limitations in (1) physical function, (2) role function, (3) social function, (4) bodily pain, (5) general mental health, (6) limitations in role function due to emotional problems, (7) vitality and (8) general health perception. A physical and a mental component summary score can be calculated. A higher score indicates a better quality of life as experienced by the patient.

Data analysis

Regarding reporting data from all studies, associations will be presented when reported in the studies. If associations were presented using Spearman's *r*, interpretation of effect size was performed using Cohen's guideline (weak ± 0.2, moderate ± 0.5, strong ± 0.8) [31]. Pooling of open source data was applied to analyze outcomes and associations. The Chi Square test was used to analyze associations between dichotomous and/or categorical variables. T-test was used to analyze a dichotomous grouping variable and continuous outcome variables, normal distribution and equality in variances being present. P-plots were used to evaluate normal distribution of data and Levene's test was used to assess the equality of variances. If there was no normal distribution of data and/or no equality in variances, Mann Whitney U analysis was performed and medians and interquartile ranges (IQR) were presented. In the statistical analysis of the open source data, PA was transformed to a dichotomous variable (presence or no presence of PA). Significance was achieved when $p<0.05$. All statistical analyses were performed using IBM SPSS, version 22.

RESULTS

Study selection

The study selection was performed in three stages. First, one reviewer (CL) retrieved 1026 articles from the patient database with the help of an information specialist. All studies where imported in RefWorks®. After removing duplicates, a total of 842 studies remained. Secondly, two reviewers (CL and TD) assessed independently titles and abstracts. A total of 110 papers remained. The same reviewers assessed the full text papers. In case of persistent disagreement a third reviewer (CS) was consulted to reach consensus. Reasons for exclusion were; not retrievable (n=1), written in Chinese language (n=3), written in Spanish (n=1), supplements or abstracts for a congress (n=11) and not meeting the inclusion criteria (n=73). Twenty studies met the inclusion criteria, of which 2 of the selected publications were conducted by the same research group en described the same patient population. One of these studies was excluded, resulting in 19 included studies (Figure 1) [32]. If this was presented in the studies, open source data was collected.

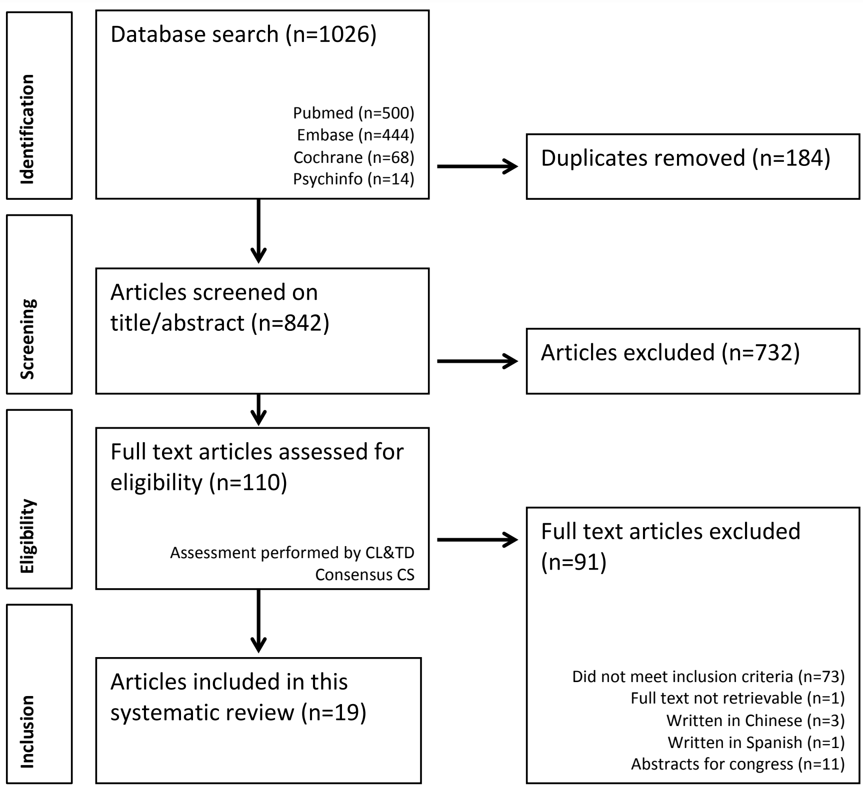

Figure 1. Flowchart of the study selection

Study and patient characteristics

All studies

The study populations of the included studies ranged from 13 to 106 patients. Eight prospective and 11 retrospective cohort studies were included. A total of 733 patients were described with a weighted mean age of 37 years (range 25-54) at time of the injury. Follow-up ranged from 13 months to 38 years (Table 3). The weighted prevalence of PA was 50% (343 of 683 patients). Seven studies were classified as high quality, nine as moderate quality and 3 of low quality according to the NOS quality assessment (Table 3) [28].

Open source

Ten studies comprised of open source data of 213 patients (169 men) with a median age of 37 years (IQR 27; 44) and median follow-up of 31 months (IQR 24; 73) (Table 4). The classification of the fracture type was described in 161 patients, with the majority having a type C3 fracture (n=74). The weighted overall prevalence of PA was 37%. Prevalence of PA after a follow-up of ≤ 36 months (range 12.5-36 months) was 31%. This was statistically significantly lower than the prevalence of PA (64%, p<.001) after a follow-up of >36 months (range 36-192 months).

Association between PA and CRO: range of motion

All studies

Three out of the 16 studies describing ROM, reported a statistically significant association between the presence of PA and diminished flexion (Table 3) [33-35]. Two of these three studies described moderate statistical significant associations (r=.350, p=.046 and r=.429, p=.016. respectively). [33,35] One study described a statistically significant lower ROM in flexion-extension arc in patients with PA grade II compared to patients with grade I PA [15]. A moderate statistically significant association between PA and poorer supination was found in one study (r=-.476, p=.029) [10]. Five studies did not find a statistically significant association between PA and ROM. [16-19,36] In the six remaining studies the association between PA and ROM was not analysed [14,29,30,37-39].

Open source

Of the 10 studies with (partially) open source data, seven had open data regarding ROM (Table 3) [10,16,19,29,33,35,37]. Pooled data analysis is presented in Table 5. Radial deviation was statistically significantly worse in the patients with PA (N=49, mean 14°, SD 6°) compared to patients without PA (N=55, mean 17°, SD 6°, p=.037). All other outcomes regarding range of motion in the patients with and without PA did not differ with statistical significance.

Association between PA and CRO: grip strength

All studies

One out of the 18 studies describing grip strength found a moderate statistically significant association between severity of PA and diminished grip strength ($r=.464$, $p=.034$) [10]. In contrast, seven studies did not find a significant association [15-19,34,36]. The remaining 10 studies did not analyse the association between PA and grip strength.

Open source

Eight studies presented open data regarding grip strength (Table 3) [10,16,19,29,30,33,35,37]. No statistically significant association between PA and grip strength was found (Table 5).

Association between PA and PROs

PROs were reported in few studies (Table 3). It was decided not to report nor perform statistical analysis on these limited results.

Predictors of PA

All studies

Eleven studies reported on predictors of PA following a DRF (Table 3). Articular incongruence (step and/or gap) at follow-up was found to be a statistically significant predictor of PA in six studies [10,12,15,33,35,39]. The weights of the associations were described as strong and moderate in two of these 11 studies (step $r=.74$, $p<.001$ and gap $r=.70$, $p<.001$; step $r=.34$, $p<.05$, respectively) [10,39]. Conflicting results on other predictive radiological factors, such as shortened radial length, dorsal angulation, radial inclination, ulnar variance and AP distance, were reported (Table 3) [11,14,39,40]. In a longitudinal study a significant progression of PA after a longer follow up duration was found (15 vs. 7 years, $p=.02$) [34]. Older age at the time of injury was associated with earlier development of PA. [11] Gender was not associated with the development of PA [13]. One study described PA to be statistically significantly less often present in patients treated surgically compared to patients treated conservatively [17]. Another study reported less PA when arthroscopically assisted surgical treatment was performed compared to non-arthroscopically assisted surgical treatment [33].

Table 3. Characteristics of the included studies

	Non open source						
	NOS	**Study type**	**Eligble N/N**	**Mean age (years)**	**Follow up (months)**	**PA**	**ROM**
Bolmers, 2013	5 MQ	PS	47	39	240	Not described	+
Foldhazy, 2007	7 HQ	PS	37/66	45	108-156	gr I: 8/66	+
Forward, 2008	5 MQ	RS	106	25	456	gr 0: 50 gr I: 31 gr II: 21 gr III: 4	- (% uninjured wrist)
Goldfarb, 2006	7 HQ	RS	16	32	180	gr 0: 0 gr I: 6 gr II: 7 gr III: 2	+
Kopylov, 1993	4 LQ	RS	76	31	384 (32 yrs)	33% PA RC 25% PA DRUJ	+
Lindau, 2000	5 MQ	PS	76	41	26	gr I: 9	+
Lutz, 2011	7 HQ	RS	81	38	108	gr 0: 2 gr I: 45 gr II: 34	+
Rogachefsky, 2001	6 MQ	RS	17	43	30	gr 0: 3 gr I: 10 gr II: 3 gr III: 1	+
Sharma, 2014	8 HQ	PS	64	OP 48 NO 52	24	NO gr I: 16 OP gr I: 5	+

Grip strength	PRO; mean	Association outcomes vs. PA	Predictors for PA
+	DASH; B#; 14 C#; 15	ROM: NS Grip strength: NS PRO: NS	-
+		ROM: NS Grip strength: NS	-
+	DASH; EA# 9 IA# 13	Grip strength: no conclusion VAS: NS DASH: no conclusion	Radial length (OR 1.21, 95% CI 1.02-1.45) Dorsal angulation (OR 1.07, 95% CI 1.03-1.1) Radial inclination: NS Intra-articular fracture (OR 3.23, 95% CI 1.43-7.14)
+		ROM: poorer F (p< .02) Grip strength: NS PRO: NS	
+		ROM: no conclusion Grip strength: no conclusion PA RC 'more complaints' than PA DRUJ, no correlation reported	Ulnar variance (2.7mm with PA vs. 0.9mm without PA, p<.01) Dorsal angulation: NS Radial inclination: NS Gender: NS
+		No conclusions	Dorsal angulation: NS Radial shortening: NS Radial inclination: NS Ulnar variance: NS Arthroscopically verified subchondral hematoma
+	DASH; 7.5	ROM: F/E: sign lower in gr II vs. gr I PA, (p=.03) Grip strength: NS VAS: NS DASH: NS	Articular (6/7 patients with step > 1mm developed severe PA) Articular cavity depth (4.1mm gr I PA vs. 5.8mm gr II PA, p<.05) AP distance (20.3mm gr I PA vs.21.7mm gr II PA, p<.05) Palmar tilt: NS Radial shortening: NS Radial inclination: NS
+		No conclusions	-
+	DASH; NO 14 OP 5	ROM: NS Grip strength: NS PRO: no conclusion	Less PA in surgically treated patients NO 16 OP 5

Table 3. Continued

	Open source						
	NOS	**Study type**	**Eligble N/N**	**Mean age (years)**	**Follow up (months)**	**PA**	**ROM**
Beyerman, 2000	6 MQ	RS, POS (no PA)	10/19	53	32.5	All < gr II	+
Catalano, 1997	5 MQ	RS, POS	21	30	86	gr 0: 5 gr I: 10 gr II: 6	+
Doi, 1999	7 HQ	PS, OS	33/82	52	31	gr 0: 16 gr I: 10 gr II: 6 gr III: 1	+
Espen, 2003	5 MQ	RS, OS	11/20	53	38	gr 0:3 >gr 0:8	+
Fernandez, 1997	8 HQ	RS, OS	31/50	49.6	28.8	1/31	-
Fitoussi, 1997	4 LQ	PS, OS	31/34	42	24	gr 0: 23 gr I: 2 gr II: 4 gr III: 2	+
Jupiter, 1993	5 MQ	RS, OS	10/13	35	30	gr 0: 9 >gr II: 1	+
Ring, 2004	7 HQ	PS, OS	18/25	46	26	gr 0: 13 gr I: 4 gr II: 1	+
Strange-Vognsen, 1991	4 LQ	RS, POS	42	29	187	gr 0: 15 gr I: 11 gr II: 9	-
Tyllianakis, 2010	5 MQ	PS, POS	6/21	53.5	13	gr 0: 3 gr I: 2 gr II: 1	+

Grip strength	PRO; mean	Association outcomes vs. PA	Predictors for PA
+	DASH; 11.5	No conclusions	-
+		ROM: supination (rho=-.476, p=.029) Grip strength (r=.463, p=.034) PRO: NS	Step (r=.74, p<.001) Gap (r=.70, p<.001)
+		ROM: F (r=-.350, p=.046) Grip strength: no conclusion	Incongruency (p<.001) Arthroscopically assisted reduction less PA (p=.014)
+	DASH; 20.5	ROM: NS Grip strength: NS PRO: NS	-
-	SF-36; PC: 46.58 MC: 53.06	PRO: With PA significant lower PC score than without PA (27.9 vs. 48.2, p<.001)	Incongruency (p<.005)
+		ROM: F (r=-.429, p=.016) Supination (r=-.423, p=.018) Grip strength: no conclusion	Incongruency > 2mm (p<.05)
+		No conclusions	-
+		ROM: NS Grip strength: NS	-
+/- (only reduced y/n)		No conclusions	Residual deformity (r=.34, p<.05) Step (r=.34, p<.05) Dorsal angulation: NS Radial inclination: NS
+		No conclusions	-

Table 3. Continued

	Open source						
	NOS	**Study type**	**Eligble N/N**	**Mean age (years)**	**Follow up (months)**	**PA**	**ROM**
Total	**7 HQ 9 MQ 4 LQ**	**7 OS 3 partially OS**	**733 (OS 213)**	**37 yrs (range 25-54)**	**range 13-456)**	**gr 0: 142 > gr 0: 343**	**15**

PA= posttraumatic arthritis (grading according to Knirk & Jupiter [8]), N=number of patients, ROM= range of motion, PRO= patient reported outcome measure, DASH= disability of arm, shoulder and hand questionnaire, NOS = Newcastle-Ottawa Scale, LQ= low quality, MQ= medium quality, HQ= high quality, PS = prospective, RS= retrospective, MA= Meta-analysis, OS= open source, POS = partially open source,

Table 4. Patient characteristics from the open source data

Characteristics	**PA (N=79) N / Median (IQR)**	**No PA (N=117) N / Median (IQR)**
Age (years)		
N	79	117
Median	36 years (27-44)	37 years (27-44)
Gender		
Male	64	92
Female	15	24
Follow up (months)		
N		
Median	46 months (24-100)	28 months (24-37)
Trauma energy		
Low energy	7	4
High energy	30	25
AO/OTA Classification		
A	3	11
B	56	10
C	59	81
Treatment		
Non-operative	18	14
Surgery	61	102
Articular incongruence at follow up (step and/or gap)		
No	8	58
Yes	51	20

Grip strength	PRO; mean	Association outcomes vs. PA	Predictors for PA
17	**9**		

EA= extra-articular, IA= intra-articular, NO= non-operative, OP= operative, NS= not significant, F= flexion, E=extension, += the study describes the outcome measurement described, -= the study does not describe the outcome measurement described, OR= odds ratio, 95% CI= 95% Confidence Interval.

Total population (N=213) N/Median (IQR)	%	Significance
213 37 yrs (27-44)		NS
169 44	79% 21%	NS
193 31 months (24-73)		*p*=.026
15 58	21% 79%	NS
11 13 147	6.4% 7.6% 86%	NS
38 174	18% 82%	*p*=.047
66 71	48% 52%	*p*<.001

Table 4. Continued

Characteristics	**PA (N=79) N / Median (IQR)**	**No PA (N=117) N / Median (IQR)**
Step (mm)		
Median	1.0 mm (1.0-2.0)	0.0 mm (0.0-1.0)
No	9	25
Yes	44	10
Gap (mm)		
Median	0.0 mm (0.0-1.0)	0.0 mm (0.0-0.0)
No	20	19
Yes	13	2
Grading PA		
Gr 0	39	84
Gr I	28	
Gr II	3	
Gr III		

N=number of patients, IQR = interquartile range, PA= posttraumatic arthritis, NS= not significant, mm=millimeter

Table 5. Open source data regarding ROM and grip strength

Range of Motion		**PA**			**No PA**			**Significance**
	N	**Mean (°)**	**SD**	**N**	**Mean (°)**	**SD**	**N**	
Flexion	124	52	18	55	52	16	69	NS
Extension	124	53	13	55	54	11	69	NS
Arc motion F/E	124	105	26	55	107	23	69	NS
Ulnar deviation	104	23	9	49	25	8	55	NS
Radial deviation	104	14	6	49	17	6	55	*p*=.037
Arc motion UD/RD	104	37	12	49	42	11	55	*p*=.063
Pronation	124	76	14	55	75	12	69	NS
Supination	124	76	15	55	81	19	69	NS
Grip strength		**PA**			**No PA**			**Significance**
	N	**Mean (%)**	**SD**		**N**	**Mean (%)**	**SD**	
% grip strength	124	79	18	55	69	79	15	NS

N=number of patients, SD= standard deviation, PA=posttraumatic arthritis, NS= not significant, F/E= dorsal flexion/extension, UD/RD= ulnar deviation/radial deviation, °=degrees, %=percentage

Total population (N=213) N/Median (IQR)	%	Significance
1.0 mm (0.0-1.7)		*p*<.001
34	39%	
54	51%	
0.0 mm (0.0-1.0)		*p*=.017
39		
15		
84	55%	
39	25%	
28	18%	
3	2%	

Open source

At a median follow up of 31 months (IQR 24; 73) 52% of the patients had some kind of articular incongruence (step and/or gap). Patients with PA experienced statistically significant more often residual articular incongruence in comparison to patients without PA (51 versus 20 patients, p<.001). Furthermore, patients with PA experienced statistically significant more often a residual step (44 versus 10 patients, p<.001) or gap (13 versus 2 patients, p=.017) (Table 4). Follow up was statistically significant longer in the patients who did develop PA (median 46 months (IQR 24; 100) versus median 28 months (IQR 24; 37), p=.026). All possible radiological predictors directly after fracture reduction and at the end of follow-up were not significantly associated with PA (Table 6).

Age at the time of injury did not differ statistically significantly between patients with and without PA (Table 3). Gender was not associated with the presence of PA. No statistical analysis on the influence of intra- versus extra-articular fracture types on PA could be performed, because only 11 patients with an extra-articular fracture were described. In the patients with intra-articular fractures, no significant difference in development of PA was seen between B and C type fractures or between C1, C2 or C3 type fractures (Table 4).

Table 6. Open source data regarding predicting radiological factors for PA

Radiological measurement		PA			No PA			Significance
	N	Mean	SD	N	Mean	SD	N	
Dorsal angulation (°)								
Postreduction	31	1	7.6	8	-3.3	9.4	23	NS
Follow-up	149	-1.3	10.2	58	-2.7	9.3	91	NS
Radial length (mm)								
Postreduction	33	10.1	5.2	8	9.9	3.7	23	NS
Follow-up	81	10.6	3.9	25	10.8	3.6	56	NS
Ulnar variance (mm)								
Postreduction	27	1.4	2.1	7	-.2	2.0	20	NS
Follow-up	98	1.0	2.3	45	.9	2.3	53	NS
Radial inclination (°)								
Postreduction	31	21.3	8.9	8	19.7	5.7	23	NS
Follow-up	148	21.5	5.1	57	21.2	4.7	91	NS

N=number of patients, SD= standard deviation, PA=posttraumatic arthritis, NS= not significant, °=degrees, %=percentage

DISCUSSION

A high prevalence of the development of PA following a DRF in non-osteoporotic patients was found (50% in all patients with a range in follow up duration of 13 months to 38 years, 37% in the open source studies after a median follow up of 31 months). Also, this study shows that the prevalence of PA seems to worsen over time (respectively 31% after a follow-up of 0-36 months versus 64% follow-up duration after 36 months). Presence of PA was statistically significantly associated with diminished radial deviation and flexion, but not with grip strength. Unfortunately, no conclusions could be drawn regarding the association between PA and PROs, because of lack of data. An intra-articular step or gap had a statistical significant negative effect on the development of PA. No further associations between radiological predictors and PA were found using open source data. Operative treatment or arthroscopically assisted surgical treatment seemed to reduce the chance of developing PA [17,33].

Prevalence of PA

The high prevalence of PA in this non-osteoporotic population is worrisome. However, from the included studies we could not derive sufficient information on the restrictions or limitations these patients experienced when executing activities of daily living, leisure time activities, work or other societal roles. Further research on PA in non-osteoporotic patients with DRF should elaborate on the impact of PA on patients' activities or participation. Since most studies comprise of small study populations and because the open source data showed that a longer follow-up duration is associated with a higher prevalence of PA, specifically open source studies may provide unique chances to gather such data. However, currently no uniform set of evaluation instruments is available, which results in difficulty of pooling data.

Association between PA and CROs

Wrist motion is dependent on complex articulations of the scaphoid, lunate and the radio carpal joint [41]. Biomechanically, flexion-extension and radio-ulnar deviation are a result of motion of the scaphoid and lunate in respect to the distal radius, which relies on the ligamentous stability between these two carpal bones and movement in the adjacent joint surfaces [42]. The majority of the DRFs in non-osteoporotic patients result from high-energy trauma and therefore frequently are intra-articular fractures. It is imaginable that the direction of the intra-articular force associated with this type of fracture causes intercarpal ligamentous injury as well as joint surface changes. Recent literature describes an incidence of 38% of associated scapholunate (SL) or lunotriquetral (LT) ligamentous injuries in distal radius fractures. [43] Associated SL or TL ligamentous injuries could be an explanation for the limited radial deviation and flexion and early PA as described in this systematic review. Furthermore, malalignment of the distal radius following a fracture can cause alterations of the distal radio-ulnar joint with anatomical change of the radio-ulnar contact area, resulting in limited pronation and supination [44]. Based on the results of this systematic review, it can be concluded that grip strength does not seem to be influenced by PA. This emphasizes that grip strength might not be an important determinant of wrist function and is not one of the first symptoms of PA, but merely a reflection of overall muscle strength and condition [45]. Ageing is typically associated with a progressive loss of skeletal muscle mass and occurs at a rate of 3-8% each decade after the age of 30 years [46,47]. Although age is a confounding factor for grip strength, our results indicate that in this relatively young group of patients grip strength is not influenced to a significant extent by age. A recent Cochrane reported on different rehabilitation methods following distal radius fractures in adults was published [48]. Twenty-six trials were included which turned out to be inhomogeneous with regards to patient characteristics (i.e. age) and were qualified as low or very low quality evidence. The authors therefore concluded that available evidence is insufficient to establish the relative effectiveness of different rehabilitation methods. It is suggested by the authors to precede rehabilitation research regarding outcome in patients with distal radius fractures with a clear aim [48]. From our systematic review it is suggested that rehabilitation in non-osteoporotic patients with distal radius fractures should have a broad approach, with special focus on wrist motion (radial deviation and flexion). Although we did not find an association between grip strength and radiological PA, it is still an important determinant of total outcome and should be addressed appropriately in rehabilitation treatment.

Associations between PA and PROs

No conclusions could be drawn regarding the association between PA and PROs, because of limited data. This is indicative of a gap in knowledge on the clinical relevance of radiological PA as measured by PROs, despite the high prevalence of PA in this group.

Predictive factors for PA

A high prevalence of PA was shown, and a longer follow-up duration was associated with a higher prevalence of PA. As such, development of PA seems to be a dynamic process and progress over time. In addition, articular incongruence was predictive for PA: patients with a step or a gap had a higher prevalence of PA. This outcome resembles the conclusions drawn in studies regarding associations between articular incongruence and PA following a DRF [10-13]. When articular incongruence is associated with the development of PA, it might be assumed that the AO classification of the fracture type would also have an association with PA. This association was not found in this study. The reason no statistical significant differences were found between AO/OTA type B and C fractures regarding the development of PA could be that inter- and intraobserver variability of the AO classification of distal radius fractures has been reported to be moderate to poor [49]. Another explanation could be that the DRFs have been surgically treated if a large incongruence was present and only the residual deformity or articular incongruence will affect the development of PA. It is hypothesized that with surgical treatment (with or without direct arthroscopic control), better anatomical reduction of the articular surface can be achieved and therefore may diminish the chance of developing PA [17,33]. Conflicting results regarding several radiological measurements predicting PA were presented in literature. However, analysis our open source data suggests that dorsal angulation, radial length, ulnar variance and radial inclination do not predict PA. These conflicting results on predicting radiological factors could be due to a substantial variability in how these factors are defined in literature. It has been suggested to develop guidelines to ensure consistency when interpreting different radiographic measurements reported in literature [50].

Strength and weaknesses

This study is the first systematic review presenting CROs and PROs and the association with PA following a DRF in non-osteoporotic patients. Because of the extent of this systematic review and the pooling of the open source data, we believe this study is a contribution to the insight in the prevalence and clinical relevance of PA in non-osteoporotic patients following a DRF. Recent literature has encouraged pooling of open source data from clinical trials and cohort studies and reporting this in systematic reviews and meta-analyses to compare outcome in a more reliable and efficient manner [51,52]. Although we believe pooling of the open source data in this systematic review contributes to the strength of the conclusions, variability between raters and the way measurements have been performed, should be acknowledged.

Some other limitations of our systematic review should be acknowledged. We have chosen an age selection criteria (men 18-59 years, women 18-49 years) in order to eliminate the risk of preexisting osteoporosis. Despite our selection criteria, some of the included patients may still have had osteoporosis. All studies included in this systematic review were cohort studies or case-control studies (level of evidence II and III) with relatively small populations and moderate methodological quality [53]. These restrictions should be taken into account when interpreting the results of this meta-analysis. In general, research in the field of rehabilitation and injuries should be more transparent by presenting open source data, especially when describing small populations, to be able to compare data in a reliable way. In addition, despite our extensive literature search, very limited data was retrieved regarding PRO. We decided not to report on these limited results and therefore no conclusions could be drawn regarding PROs following DRFs in non-osteoporotic patients. Furthermore, a new scoring method was used to assess the methodological quality of the studies, with equal weights for each quality category, except for the comparability category [28]. It could be argued that the quality categories should be scored separately instead of a combined total score in order to provide optimal insight into the quality of the different studies. Most included studies reported statistical significance of their results, but the weight of the associations was poorly described. Several authors have described associations between the residual articular incongruence and PA.

Further research

The high prevalence rate of PA found in the (pooled) data shows that investigation of outcome in non-osteoporotic patients with a long active and working life ahead should have more attention. To direct treatment strategy, rehabilitation and to decide what an acceptable level of rehabilitation is in the follow-up of non-osteoporotic patients with a DRF there is a need for a reliable interpretation of

PROs and the association with PA investigated by using randomized controlled trials with or without implementing pooling of open source data. For patients and therapists it would be of great value to be able to work towards an evidence-based rehabilitation goal. It would also be very beneficial to gain more insight in the influence of radiological characteristics following fracture reduction, such as radial shortening and radial inclination on CROs, PROs and PA.

Conclusions

Half of all non-osteoporotic patients developed some degree of PA following a DRF. Also, PA seems to progress over time. PA following a distal radial fracture was associated with a limited radial deviation and flexion, but not with grip strength. This suggests that rehabilitation should have a broad approach, with focus on wrist motion, and on learning to adjust daily activities to limited wrist motion to optimize functional recovery. Unfortunately no conclusions could be drawn regarding PROs and their clinical applicability in the follow up of DRF in non-osteoporotic patients, because of limited data. PROs should be investigated more thoroughly to be able to understand the value of using these instruments in interpreting outcome in follow up of these non-osteoporotic patients. Further research could produce evidence-based rehabilitation goals for patients and therapists. Treatment of DRF should be directed at avoiding articular incongruence, because of its statistically significant association with the development of PA. Conflicting results in literature have been reported on dorsal angulation, radial length, ulnar variance and radial inclination on predicting PA. More thorough research on other radiological factors predicting PA could show more insight on primary treatment goals to avoid PA in the follow up of these young non-osteoporotic patients.

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CHAPTER 3

Prevalence of posttraumatic arthritis following distal radius fractures in non-osteoporotic patients and the association with radiological measurements, clinician and patient reported outcomes

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ABSTRACT

Introduction. Outcomes of non-osteoporotic patients who sustained a distal radius fracture (DRF) have not gained much attention in recent literature. Aims of this study were to determine prevalence of posttraumatic arthritis (PA), to analyze associations of radiological measurements, clinician and patient reported outcomes (CROs and PROs) with PA and gain insight in employment changes after DRF in non-osteoporotic patients.

Methods. Non-osteoporotic patients following a DRF were selected. Radiographs of both wrists were obtained at follow-up and the degree of PA was determined. Radiological measurements consisted of grading of PA, ulnar variance, radial length, radial inclination, dorsal tilt, distal radio-ulnar joint width, scapholunate dissociation, step-off and gap. Active range of motion and grip strength measurements were performed and all patients filled in 4 questionnaires to assess pain, upper extremity functioning, and health status (Disability of Arm, Shoulder and Hand; Patient Reported Wrist Evaluation; Michigan Hand Questionnaire; Short Form-36).

Results. Seventy-three patients (32 women, 41 men) with a mean age of 33.5 (SD 9.2) years were included. Prevalence of PA was 32% at a median follow-up of 62.0 months. Patients with PA had statistically significant longer radial length (1.1mm, 95% CI -2.1; -.0, p=.045). Patients with PA had a statistically significant diminished flexion/extension arc of motion (12.0°, p=.008) and ulnar/radial deviation arc of motion (6.3°, p=.018). When corrected for dominance, all grip strength measurements were not statistically significant different between patients with and without PA. Statistically significant poorer PROs in patients with PA were the MHQ subscales general functioning (65 vs. 75, p=.018), esthetics (94 vs. 100, p=.037), satisfaction (75 vs. 92, p=.042) and total score of the MHQ (83 vs. 91, p=.044), as well as the SF-36 subscale physical functioning (95 vs. 100, p=.028). In regression analyses the DASH, PRWE function and PRWE total were statistically significant associated with flexion/extension arc of motion. Seven patients (10%) changed or left their occupation because of the DRF.

Conclusions. Non-osteoporotic patients had a considerably high prevalence of PA following DRFs, despite relatively short follow-up time. Patients with longer radial length more often had PA. Irrespective of AO/OTA fracture type, patients with PA had diminished range of motion, but no altered grip strength measurements. Non-osteoporotic patients following DRFs perceived diminished general functioning and dissatisfaction, which was impacted by the diminished active range of motion. Pain or impaired general health status were not reported. The PRO MHQ might be a valuable evaluation tool in this patient group. Change of occupation following DRFs should have attention in further research.

INTRODUCTION

The development of posttraumatic arthritis (PA) following distal radius fractures (DRFs) has been described in populations with a wide range in age and follow-up time [1]. Clinical studies have supported the hypothesis that an increasing age is an important risk factor for the development of PA [2]. However, already in non-osteoporotic patients the prevalence of PA following DRFs has been described as high as 43% to 50% [3,4]. Since DRFs in young non-osteoporotic patients usually result from high energy trauma, these injuries often have intra-articular involvement [5]. This can result in residual articular incongruence, which is usually described in step-offs and gaps [6-11]. Intercarpal ligamentous injuries, radiologically reflected in the distance between scaphoid and lunate (SL ligament injury) and distal radio-ulnar joint instability are also associated with DRFs [5,12,13]. Conflicting results have been reported in literature with regard to other radiological parameters and their association with the development of PA in heterogeneous cohorts [4-6,10,14]. PA following a DRF has been associated with diminished clinician reported outcomes (CROs), such as active range of motion and strength measurements, in populations with wide age ranges [4-6,15,16]. Also, an association between PA following DRF and poorer patient reported outcomes (PROs), assessed by the Short Form Health Survey-36 (SF-36) in patients with an age range of 24 to 93 years has been reported [17]. Other studies did not find an association between PROs and PA [11,18,19]. Literature suggests that patients with pre-existing osteoporosis who sustained a DRF have better PROs than those without osteoporosis [20,21]. In addition to pre-existing osteoporosis, age seems to be an independent factor influencing PROs following DRFs [2].

Few studies report on non-osteoporotic study populations following DRFs [22,23]. As a consequence, limited information is available on the long-term outcomes of non-osteoporotic patients following a DRF. Although high prevalence of PA is reported in literature in non-osteoporotic patients after DRF, associations with CROs and PROs remain unclear. We hypothesized that PA following DRFs in non-osteoporotic patients may have greater impact because an active (working) life may pose higher demands on wrist function compared to older patients. Therefore, insight in the association between radiological measurements and PA and the association between PA and wrist function, activity performance, pain, satisfaction, quality of life in these young patients is mandatory. This knowledge could be used to direct rehabilitation treatment and to inform young patients on outcomes and influence on societal roles (e.g. occupation) they can expect in the long-term.

Objectives

The aims of this study were to determine the prevalence of PA, and to analyze associations of radiological measurements, CROs and PROs with PA and gain insight in employment changes following a DRF in non-osteoporotic patients.

METHODS

This retrospective cohort study was approved by the Medical Ethics Committee (NL41587.099.13) and registered at the Dutch Trial Bureau (TC 4002). Before entering the study, participants signed an informed consent form. From a level II trauma center database, we selected all patients of a non-osteoporotic age group (men, 18-50 years and women, 18-40 years old, at the time of injury) who sustained a DRF between January 2005 and January 2011 and were treated non-surgically or surgically [24-26]. Exclusion criteria were fractures treated surgically after the 7th day following injury, open fractures, pre-existing osteoarthritis or risk factors for early osteoporosis (steroid use, alcoholism or early menopause, low body weight), because outcomes in these patients might not be representative for young non-osteoporotic patients following a DRF. A total of 433 patients fulfilled the inclusion criteria and received an invitation to participate in the study. A notification of changed home address was received from 43 participants, but current addresses could not be retrieved. From 306 patients, no response was received. Eighty-four patients responded of which 73 (32 women, 41 men) consented to participate. All eligible patients were invited for a single visit to the rehabilitation department. One hand therapist measured CROs (active range of motion and grip strength). Patients also filled in four PROs at the time of their visit. At the time of the participants' visit, lateral (Lundy) and posteroanterior (PA) wrist radiographs were made of both wrists. All radiographs were evaluated by a single radiologist specialized in musculoskeletal disorders with a special interest in hand and wrist anatomy. PA was classified according to the grading system as described by Knirk and Jupiter: 0= no signs of PA, I=slight joint-space narrowing, II=marked joint-space narrowing and osteophyte formation, III=bone-on-bone, osteophyte and cyst formation [1]. Further radiological parameters were measured according to the technique described by Kreder *et al*; ulnar variance, radial length, radial inclination and dorsal angulation (Figure 1) and step-off and gap (Figure 2) [27,28]. In addition, the scapholunate distance (SL distance) and the distal radio-ulnar joint (DRUJ) space were measured [29]. Normal ranges for radiological factors have been previously described; ulnar variance -4 to 2mm [30,31], radial length 8-17mm [30], radial inclination 16-29° [32,33], dorsal angulation 0-palmar 22° [34,35]. In addition, to correct for anatomical variation between patients, measurements of the uninjured wrist were obtained at follow up and used as a reference to interpret measurements of the injured wrist.

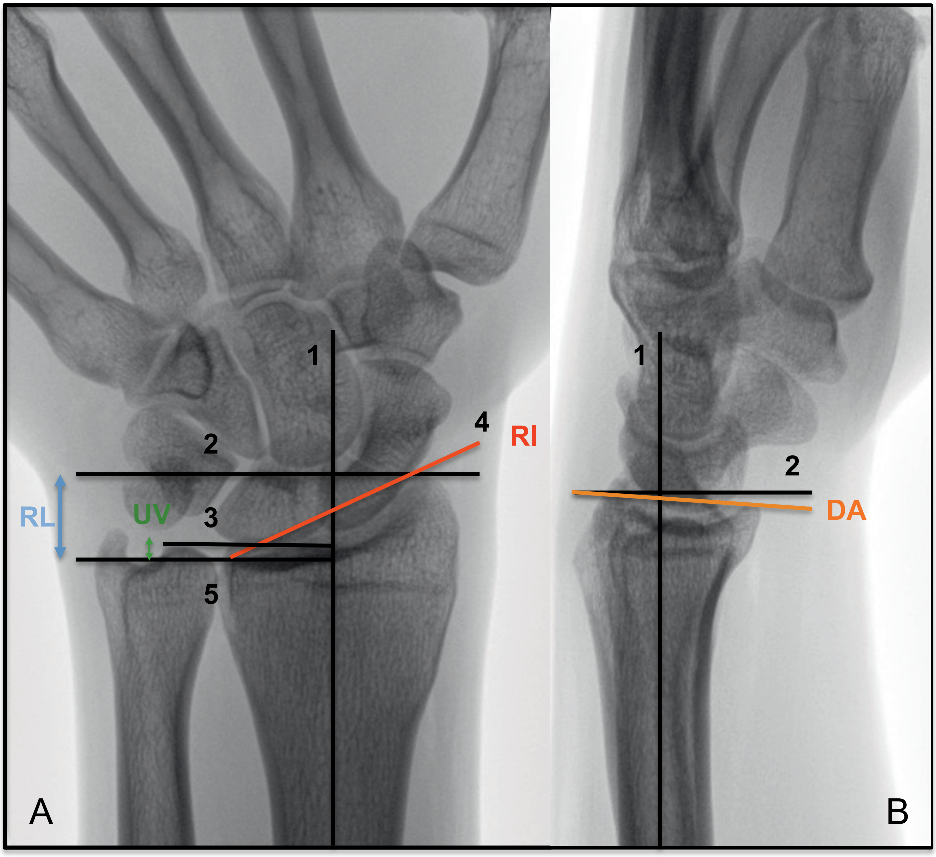

Figure 1. (A) Posteroanterior measurement guidelines: (1) The center of the radial shaft is determined at 3cm and 5cm below the mid-region of the proximal lunate articular surface. This line represents the central axis of the radius. (2) A line perpendicular to the central long axis of the radius is drawn at the level of the most distal aspect of the radial articular surface. (3) A line perpendicular to the central long axis of the radius is drawn at the level of the ulnar margin of the distal radial articular surface. (4) The radial and ulnar margins of the distal radial articular surface are connected. (5) A line perpendicular to the central long axis of the radius is drawn at the level of the distal ulnar articular surface. (B) Lateral measurement guidelines: (1) The center of the radial shaft is determined at 3 cm and 5 cm below the mid-region of the proximal lunate articular surface. This line represents the central long axis of the radius. (2) A line perpendicular to the central long axis of the radius is drawn at a convenient level. (3) The dorsal and anterior margins of the distal radial articular surface are connected. UV=ulnar variation, RL=radial length, RI=radial inclination, DT=dorsal tilt.

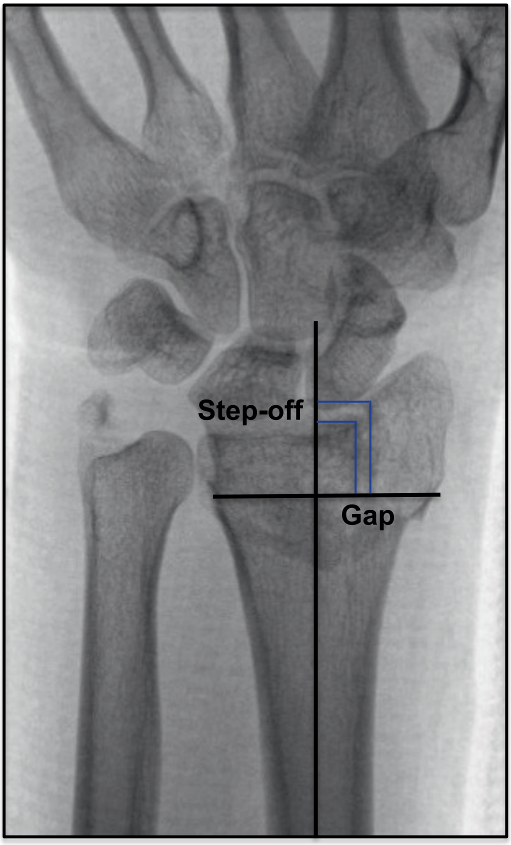

Figure 2. Step-off and gap measurement. (1) Step-off at the articular surface of the distal radius was measured parallel to the central long axis of the radius by drawing perpendicular lines from the most distal margin of each side of the articular incongruence. (2) Gap deformity was measured along a perpendicular line to the central long axis of the radius.

Clinician reported outcomes: active range of motion and grip strength

The participants were positioned sitting at a table, with hips and knees flexed 90˚. Elbows were positioned on the table and flexed in 90˚ with wrists in neutral position. A digital protractor of Biometrics LTD and E-Link® software was used to measure active range of motion. Flexion/extension arc of motion, ulnar/radial deviation arc of motion and supination/pronation arc of motion were measured in degrees. Grip strength and sustained grip strength were measured in kilograms using a digital Jamar dynamometer and key pinch strength using a pinch meter of Biometrics LTD and E-Link® software. For people with right sided dominance it is known that the right hand has 10% more grip strength in comparison to the left hand. This is not the case when people are left sided dominant; grip strength in both hands is similar [36]. Therefore, a correction for grip strength measurements was performed to correct for right sided dominance. Grip strength of the injured wrist was calculated as a percentage of the uninjured wrist to correct for variation between patients. For assessing sustained grip strength, patients were asked to grip as hard as possible during a 30 second period, the average grip strength (kilograms), computed over the last 18 seconds of this 30-second period was recorded. Key pinch strength measured in kilograms was derived from the maximum peak strength sustained during at least 2 seconds. The mean of three performances was presented for all strength measurements. First, all active range of motion measurements were recorded. Subsequently grip strength, sustained grip strength and key pinch strength were assessed in consecutive order, alternating dominant and non-dominant sides.

Patient reported outcomes: DASH, PRWE, MHQ, SF-36

All patients completed 4 questionnaires involving pain scores, specific upper extremity functioning, and health status.

The Disability of Arm, Shoulder and Hand (DASH) Questionnaire is a 30-item self-report measure assessing physical functioning and symptoms of the upper limb. DASH-scores range from 0 to 100 (higher scores indicate worse function). The DASH has a good validity, reliability and responsiveness in upper extremity disability assessment [37,38].

The Patient Rated Outcome Evaluation (PRWE) is a 15-item questionnaire divided into two subscales: pain (5 items) and function (10 items). The PRWE was developed to assess pain and functioning in patients with DRFs [39]. The pain items were selected to represent the total spectrum of frequency and intensity. The function items were selected to represent a range of physical activities that require different ranges of motions or muscle strength capabilities. For both subscales the maximum score is 50 (most disability) and the minimum score is 0 (no disability). Although these subscales have been reported frequently in literature, it has been suggested that the PRWE measures a single dimensional trait, and a single (sum) score should be used [40]. The questionnaire has a good validity for symptoms and function of the wrist [41].

The Michigan Hand Outcomes Questionnaire (MHQ) assesses hand outcomes that are of importance to patients and specific for the impaired hand (left and right separately) and includes 6 subscales (general function, activities of general life, work, pain, esthetics and satisfaction). The subscale score is the sum of the outcome of each question and ranges from 0 to 100. A higher score on the pain subscale indicates less pain. For the other five subscales and the total score higher scores imply a better function. The MHQ compares favourably with other PROs regarding upper extremity in the area of test-retest reliability, validity and responsiveness. In addition it has high internal consistency [42]. The strength of the MHQ is its multidimensional construct in measuring symptoms, function, aesthetics and satisfaction [42].

The SF-36 is developed to survey overall health status [43]. It contains 36 questions to assess limitations in (1) physical function, (2) role function, (3) social function, (4) bodily pain, (5) general mental health, (6) limitations in role function due to emotional problems, (7) vitality and (8) general health perception. Scale scores range from 0 to 100 with higher scores indicating a better health status. Scale scores can be used to calculate a physical and a mental component summary score [43]. Validity of this questionnaire is sufficient for groups reporting varying extents of illness-health [44].

Work

The intensity of executing work tasks was categorized according to the Dictionary of Occupational Titles (DOT) classification in sedentary, light, medium, heavy or very heavy work [45]. Patients filled in a short questionnaire to report change of work following the DRF and the reason for such a change.

Statistics

Data were assessed for normal distribution. Continuous data were presented as mean (standard deviation, SD) and as median (interquartile range, IQR) when no normal distribution of the data was present. The Chi Squared test and Fisher's exact tests were used to analyze associations between dichotomous and/or categorical variables. T-tests were performed when analyzing continuous variables if a normal distribution was found. If data did not have a normal distribution, Mann Whitney U tests were used. One way ANOVA tests were performed when analyzing the association between continuous variables and categorical variables, Bonferroni posthoc analyses were performed afterwards. Multivariable linear regression analysis, using backward stepwise selection (until all *p*-values were ≤ 0.2) was performed with PROs as an outcome and other factors (age, gender, AO/OTA fracture type, type of treatment, follow-up, flexion-extension arc of motion, grip strength and presence of PA) as explanatory variables. To be able to impute the categorical variable AO/OTA fracture type In regression analysis, 2 dummy variables were calculated with AO/OTA fracture type A as reference variable (dummy1 is AO/OTA fracture type B=1, other types=0; dummy2 is AO/OTA fracture type C=1, other types=0). Level of significance was set at $p \leq 0.05$. All statistical analyses were performed using IBM SPSS, version 22.

RESULTS

Eighty-four patients of the 433 eligible patients responded to the invitation to participate in the study of which 73 (32 women, 41 men) consented to participate with a mean age of 33.5 (SD 9.2) years at the time of the injury (participation rate 19%) (Table 1). Participants suffered statistically significant more often from intra-articular fractures according to the AO foundation and Orthopaedic Trauma Association (AO/OTA) classification system than non-participants. Of the participants, 19.2% had type A fractures, 41.1% type B and 39.7% type C fractures. In contrast, of the non-participants 53.1% had type A fractures, 28.6% type B and 18.3% type C fractures (p=.013). No further differences between participants and non-participants were found.

Prevalence of PA

After a median follow up of five years (62.0 months) the prevalence of PA (grade I, II) was 32% (Table 1). Patients with PA were more often males (73.9% versus 48.0%) and statistically significant older (6.6 years) than patients without PA (Table 1). No statistically significant differences between patients with and without PA regarding trauma energy, type of treatment, AO/OTA fracture classification or dominance were found (Table 1). Patients who were treated surgically, more often had AO/OTA type C fractures in comparison to patients who were treated conservatively (AO/OTA type A 1, type B 0, type C 27 surgically treated, AO/OTA type A 8, type B 18, type C 19 conservatively treated).

PA and radiological measurements

All radiological measurements were within normal ranges [30-35]. Between patients who were treated surgically and patients who were treated conservatively (with our without closed reduction), no statistically significant difference in radiological measurements were found at follow up. When comparing the radiological measurements of the injured to the uninjured wrist at follow up, only dorsal angulation was statistically significant more pronounced in the injured wrist (-1.3° versus 5.1°, p<.001) (Table 2). Patients with PA had a statistically significant longer radial length at follow up (13.7mm versus 12.6mm, p=.045) (Table 3). Also, the difference in radial length between the injured and uninjured wrist was greater in patients with PA (.6 versus -.6, p=.024). All other radiological measurements at follow up did not differ between the patients with and without PA (Table 3).

Table 1. Patient characteristics of the total population and differences between patients with and without PA. Results of independent samples T-test (age) and Chi- squared test (other variables)

	Total population (N=73)	**PA (N=23)**
Age at time of the injury (years)		
Mean (SD)	33.5 (9.2)	38.0 (8.6)
Follow up (months)		
Median (IQR)	62.0 (53.0;84.5)	70.0 (56.0;84.0)
	N (%)	**N (%)**
Gender Male	41 (56.2)	17 (73.9)
Energy trauma		
Low energy	20 (27.4)	3 (13.0)
High energy	45 (61.6)	16 (69.6)
Unknown	8 (11.0)	4 (17.4)
AO/OTA Classification		
A	14 (19.2)	3 (13.0)
B	30 (41.1)	8 (34.8)
C	29 (39.7)	12 (52.2)
Dominant hand injured	37 (50.7)	9 (39.1)
Treatment		
Cast	33 (45.2)	7 (30.4)
Closed reduction/cast	12 (16.4)	4 (17.4)
Surgical	28 (38.4)	12 (52.2)
Grading PA		
Gr 0	50 (68.5)	0
Gr I	13 (17.8)	13
Gr II	10 (13.7)	10
Gr III	0 (0.0)	0

N= number of patients, SD= standard deviation, IQR = interquartile range, PA= posttraumatic arthritis, 95% CI= 95% Confidence Interval, fracture type A, B and C according to the AO foundation and Orthopaedic Trauma Association AO/OTA classification, PA= posttraumatic arthritis, *= statistical significance.

No PA (N=50)	Difference in means (95% CI)	*p*-value
31.4 (8.9)	6.6 (2.1; 10.9)	.004*
62.0 (52.8;85.0)		.771
N (%)		
24 (48.0)		.038*
17 (34.0)		.150
29 (58.0)		
4 (8.0)		
11 (22.0)		.357
22 (44.0)		
17 (34.0)		
28 (56.0)		.180
26 (52.0)		.100
8 (16.0)		
16 (32.0)		
50		
0		
0		
0		

Clinician reported outcomes

Active range of motion

Patients with PA had statistically significant diminished flexion/extension arc of motion (12°, p=.008) and ulnar/radial deviation arc of motion (6.3**°,** p=.018) compared to patients without PA (Table 4).

AO/OTA fracture classification was not statistically significant associated with active range of motion (Table 5).

Grip strength

Compared to patients without PA, the grip strength and key pinch strength were 9.3% and respectively 8.8% weaker (p=.032 and p=.015) in patients with PA (Table 4). However, when correcting for dominance with the 10% rule, no statistically significant differences in grip strength measurements are present between patients with and without PA (Table 4).

Patient reported outcomes

The median scores of the MHQ subscales: general functioning (65.0 compared to 75.0, p=.018), esthetics (93.8 compared to 100.0, p=.037) and satisfaction (75.0 compared to 91.7, p=.042) were statistically significant poorer in the patients with PA (Table 6). Also, the median total MHQ score was statistically significant poorer in patients with PA (83.0 compared to 90.5, p=.044) (Table 4). Regarding the SF-36, physical functioning (median 95.0 versus 100.0, p=.028) was statistically significant poorer in patients with PA.

Table 2. Radiological measurements at follow up compared with the measurements of the uninjured wrist at follow-up. Results of paired samples T test

		Follow up injured wrist		**Follow-up uninjured wrist**			**Significance**
Radiological factors	**N**	**Mean**	**SD**	**Mean**	**SD**	**Mean difference (SD)**	***p*-value (95% CI of mean difference)**
Ulnar variance (mm)	73	.9	1.8	.4	1.6	.4 (1.9)	.063 (-.0; .9)
Radial length (mm)	73	13.0	2.1	13.2	2.1	-.2 (2.1)	.318 (-.7; .2)
Radial inclination (°)	73	25.5	3.6	26.4	3.8	-.9 (4.2)	.079 (-1.9; -.1)
Dorsal angulation (°)	73	-1.3	6.6	-5.1	4.1	3.8 (6.5)	<.001 (2.3; 5.3)*
SL distance (mm)	45	2.1	.4	2.0	.4	.1 (.5)	.099 (-.0; .3)
DRUJ distance (mm)	72	2.4	.8	2.3	.8	.1 (.7)	.224 (-0.1; .3)

N=number of patients, SD= standard deviation, 95% CI=95% confidence interval, *=significant difference, SL=scapholunate ligament, DRUJ= distal radioulnar Joint, °=degrees, mm=millimeter

Table 3. Associations between radiological measurements and PA. Outcome of Independent T-test and Mann Whitney U

Radiological factors	PA (N=23)		No PA (N=50)		Significance
	Mean	**SD**	**Mean**	**SD**	***p*-value (95% CI of mean difference)**
Ulnar variance (mm)	1.1 (N=23)	2.4	0.7 (n=50)	1.5	.462 (-1.5;.7)
Radial length (mm)	13.7 (N=23)	2.5	12.6 (n=50)	1.9	.045* (-2.1;-.0)
Radial inclination (°)	25.6 (N=23)	4.4	25.5 (n=50)	3.2	.888 (-1.9;1.7)
Dorsal angulation (°)	-2.2 (N=23)	8.0	-0.9 (n=50)	5.9	.472 (-2.4;5.2)
SL distance (mm)	2.3 (N=16)	0.4	2.1 (n=38)	0.4	.072 (-.4;.0)
	Median	**IQR**	**Median**	**IQR**	**Mann Whitney U *p*-value**
DRUJ distance (mm)	2.1 (N23)	1.8;2.9	2.3 (n=50)	1.9;2.8	.533
Step-off (mm)	0.0 (N=16)	.0;.0	0.0 (n=38)	.0;.0	.053
Gap (mm)	0.0 (N=15)	.0;.0	0.0 (n=39)	.0;.0	.177

N=number of patients, SD= standard deviation, 95% CI=95% confidence interval, *=significant difference, SL=scapholunate ligament, DRUJ= distal radioulnar Joint, °=degrees, mm=millimeter

Table 4. CROs: differences between patients with and without PA. Results of independent samples T-test

CROs	PA (N=23) Mean (SD)	No PA (N=50) Mean (SD)	Difference in means (95% CI)	*p*-value
Active range of motion (°)				
Flexion/extension arc	133.1 (17.8)	145.1 (17.3)	12.0 (3.2; 20.7)	.008*
Ulnar/radial deviation arc	53.7 (9.4)	60.1 (10.7)	6.3 (1.1; 11.5)	.018*
Pro/supination arc	144.8 (14.2)	147.6 (12.4)	2.8 (-3.7; 9.3)	.397
Grip strength not corrected for dominance (% of the uninjured wrist)				
Grip strength	88.0 (15.7)	97.3 (17.4)	9.3 (.8; 17.8)	.032*
Sustained grip	90.3 (18.3)	98.9 (26.4)	8.6 (-3.6; 20.8)	.165
Key pinch strength	89.4 (18.0)	98.2 (11.6)	8.8 (.4; 17.1)	.015*
Grip strength corrected for dominance (% of the uninjured wrist)				
Grip strength	89.6 (11.8)	97.3 (16.7)	7.7 (-.1; 15.4)	.052
Sustained grip	92.2 (17.9)	98.7 (28.5)	6.5 (-6.3; 19.4)	.315
Key pinch strength	115.5 (121.1)	108.7 (74.6)	-6.8 (-52.8; 39.2)	.769

N= number of patients, SD= standard deviation, **°**= degrees, %= percentage, PA= posttraumatic arthritis, 95% CI= 95% Confidence Interval, *= statistical significance.

Table 5. Associations between AO/OTA classification and active range of motion. Results of one way ANOVA and posthoc Bonferroni tests

	One way ANOVA Active range of motion (°)			
AO/OTA classification	**Type A Mean (SD)**	**Type B Mean (SD)**	**Type C Mean (SD)**	***p*-value**
Flexion/extension arc	150.1 (17.0)	139.1 (19.2)	139.2 (16.9)	.128
Ulnar/radial deviation arc	56.7 (9.8)	57.6 (12.2)	59.2 (9.7)	.742
Pro/supination arc	150.0 (10.3)	146.3 (12.8)	145.5 (14.4)	.563

SD= standard deviation, °= degrees, 95% SE=standard error

Table 6. PROs: differences between patients with and without PA. Results of Mann-Whitney U test

PROs	**PA (N=23) Median (IQR)**
DASH	6.7 (2.5; 24.2)
PRWE	
Pain	8.0 (0.0; 15.0)
Function	10.0 (2.0; 18.0)
Total	13.0 (3.5; 21.0)
MHQ	
General function	65.0 (50.0; 80.0)
Activities general life	95.0 (80.0; 100.0)
Work	100.0 (80.0; 100.0)
Pain	85.0 (75.0; 100.0)
Esthetics	93.8 (68.8; 100.0)
Satisfaction	75.0 (41.7; 95.8)
Total	83.0 (67.1; 91.0)
SF-36	
Physical functioning	95.0 (75.0; 95.0)
Social functioning	100.0 (87.5; 100.0)
Rolemodel physical problem	100.0 (50.0; 100.0)
Rolemodel emotional problem	100.0 (100.0; 100.0)
Mental health	88.0 (80.0; 92.0)
Vitality	75.0 (60.0; 85.0)
Pain	89.8 (67.3; 100.0)
General health experience	80.0 (65.0; 85.0)
Health change	50.0 (50.0; 50.0)
Physical Component	88.7 (69.3; 95.0)
Mental Component	87.6 (83.4; 94.3)

N= number of patients, IQR= interquartile range, PA= posttraumatic arthritis, VAS= Visual Analogue Scale, DASH= disability of Arm, Shoulder and Hand questionnaire, PRWE= Patient Rated Wrist Evaluation, MHQ= Michigan Hand Questionnaire, SF-36= Short Form (36) Health Survey, *= statistical significance.

Posthoc Bonferroni Difference in means (SE)					
A vs B	*p*-value	A vs C	*p*-value	B vs C	*p*-value
11.0 (5.8)	.074	10.9 (5.8)	.434	-.1 (4.7)	1.00
-.9 (3.5)	1.00	-2.5 (3.5)	1.00	-1.6 (2.8)	1.00
3.7 (4.2)	1.00	4.5 (4.3)	.887	.8 (3.4)	1.00

No PA (N=50) Median (IQR)	Difference in medians	*p*-value
3.3 (.6; 11.8)	3.4	.094
5.5 (0.0; 14.5)	2.5	.661
4.5 (0.0; 12.0)	5.5	.187
8.3 (1.4; 20.1)	4.7	.424
75.0 (65.0; 95.0)	10.0	.018*
100.0 (85.0; 100.0)	5.0	.189
95.0 (88.8; 100.0)	5.0	.789
90.0 (80.0; 100.0)	5.0	.248
100.0 (93.8; 100.0)	6.4	.037*
91.7 (70.8; 100.0)	16.7	.042*
90.5 (81.0; 95.5)	7.5	.044*
100.0 (90.0; 100.0)	5.0	.028*
100.0 (87.5; 100.0)	0.0	.889
100.0 (100.0; 100.0)	0.0	.226
100.0 (100.0; 100.0)	0.0	.474
84.0 (75.0; 92.0)	4.0	.469
70.4 (60.0; 85.0)	4.6	.650
79.6 (67.3; 100.0)	10.2	.942
72.5 (63.8; 85.0)	7.5	.277
50.0 (50.0; 63.8)	0.0	.442
88.4 (81.0; 92.5)	.3	.972
89.2 (79.1; 93.1)	1.6	.669

Regression analysis

Flexion/extension arc of motion was a statistically significant explanatory variable for DASH, PRWE function and PRWE total. Although not statistically significant, flexion/extension arc of motion did seem to be an important explanatory variable for the PRWE pain and MHQ total (Table 7). Percentage of grip strength was an explanatory variable in the linear regression models of the total MHQ score. Type of treatment and AO/OTA fracture type were not statistically significant explanatory variables for all PROs. Regarding the regression analysis of the SF-36 physical component score, all variables were removed, because no association with *p*-values <.200 were present (Table 7).

Table 7. Linear regression analyses regarding PROs and explanatory variables

Dependent	Explanatory variables	Regression coefficient (SE)	*p*-value
DASH	Gender	-4.5 (2.8)	.112
	Follow-up time	-.2 (.1)	.033
	Flexion/extension arc	-.2 (.1)	.017
PRWE pain	Follow-up time	-.1 (.1)	.076
	Flexion/extension arc	-.1 (.1)	.103
PRWE function	Gender	-8.3 (3.5)	.023
	Follow-up time	-.2 (.1)	.090
	Flexion/extension arc	-.2 (.1)	.013
PRWE total	Gender	-5.8 (4.1)	.164
	Follow-up time	-.2 (.1)	.058
	Flexion/extension arc	-.3 (.1)	.029
MHQ total	Flexion/extension arc	.2 (.1)	.118
	% Grip strength	.3 (.1)	.027
SF 36 physical component	-	-	-
SF 36 mental component	Treatment	9.7 (3.7)	.011

PRO=patient rated outcome measure, MHQ=Michigan Hand Outcomes Questionnaire, SF-36=Short Form 36 questionnaire, SE= standard error, % grip strength= percentage grip strength of the affected compared to the non affected wrist

Work

Seven patients (10%) changed or left their occupation, all because of the DRF. Four of them had signs of PA. All of them changed to less demanding work or became unemployed. Change of occupation was more prevalent in patients in physically demanding jobs pre-injury; 3 of the 6 patients with heavy occupation (50%), 2 of 18 patients with medium occupation (11%), 1 of 15 with light occupation (7%) and 1 of 29 patients with sedentary occupation (3%) changed.

DISCUSSION

A high prevalence of PA following a DRF in young non-osteoporotic patients was found (32%). Patients with PA had statistically significant longer radial length than patients without PA. Within the group of patients with PA, radial length was also longer in comparison to the uninjured wrist. Patients healed with a residual gap more often had PA. PA was associated with diminished flexion/ extension arc of motion and ulnar/radial deviation arc of motion. Patients healed with a residual gap more often had PA. When corrected for dominance, no statistically significant differences in grip strength measurements between patients with and without PA are present. In patients with PA the subscales 'general functioning', 'esthetics' and 'satisfaction' from the MHQ questionnaire were statistically significant poorer, as was the total MHQ score and the physical functioning scale of the SF-36. The DASH, PRWE function and PRWE total were statistically significant impacted by flexion/extension arc of motion.

Prevalence of PA

The high prevalence of PA of 32% after a median follow-up of 5 years in this young population was surprising. Forward et al presented a prevalence of 43% after a mean follow up of 38 years in non-osteoporotic patients at time of the injury [4]. The prevalence in our study might be overestimated due to the low response rate, as individuals with complaints might be more interested in participating in research activities. This assumption is supported by the fact that participants had sustained more intra-articular DRFs than non-participants. Further research on the prevalence of PA after DRFs in young patients is needed.

Radiological measurements

DRFs in non-osteoporotic patients mainly result from high-energy trauma and therefore frequently lead to intra-articular fractures [46]. Our results are supported by literature, suggesting that DRFs that healed with a residual gap and/or overall intra-articular incongruence of ≥ 2 mm are associated with early radiographic signs of PA [3,4,47-49]. In addition, a systematic review recently published by our research group established that other radiological predicting factors for PA such as radial length, radial inclination, dorsal angulation and ulnar variance are presented in literature with conflicting results [3]. Regarding radiological measurements, only radial length was 1.1mm longer at follow up in patients with PA in comparison to patients without PA. All studies reporting on the influence of radial length, reported on shortening of radial length. Most studies reported no statistically significant association with shortened radial length and the development of PA [1,5,50], except for Forward *et al.* [4]. The development of PA has multifactorial causes, such as increased stress on the articular surface that damages cells and matrices of articular cartilage and subchondral bone [2]. Overcorrection of the radial length can cause higher axial loading on the articular surface of the distal radius and therefore may contribute to the development of PA [51,52]. In previous literature normal ranges for radiological factors have been described; ulnar variance -4 to 2mm [30,31], radial length 8-17mm [32], radial inclination 16-29° [30,33], dorsal angulation 0-palmar 22° [34,35]. All measurements in this study were within these normal ranges. Although radial length seems to influence the development of PA, more research regarding these radiological predicting factors for PA is mandatory to provide constructive conclusions. Common held beliefs are dictated by the findings stated earlier that anatomical reduction of articular surfaces and absolute stable internal fixation should be pursued. In this study, no statistically significant difference regarding presence of PA between patients who were treated conservatively and operatively was found. This could suggest that anatomical reduction was achieved when patients were treated surgically and little residual incongruence was present following treatment. The relatively short follow-up period (5 years) in our study should preferably be extended in further research to get insight in the 'natural' course of PA in young patients with DRF. With regard to CROs, it has been reported that presence of PA did not influence aROM and grip strength after 15 year follow up [53]. However, the impact of PA after long term follow up on participation in societal roles and in the personal lives of these young people, captured with PROs remains unclear.

Clinician reported outcomes

Patients with PA showed a diminished flexion/extension arc and ulnar/radial deviation arc of motion. It is known that residual articular incongruence affects aROM already after a follow up of 1 year [54]. Other authors have shown that patients can maintain a high level of functioning with PA [53]. Articular incongruency is the logical result from intra-articular fractures, however in our study no statistically significant association between fracture severity as depicted by the AO/OTA classification and active range of motion was found. In addition, associated intercarpal ligamentous injuries are known to influence active range of motion following DRFs and could be an explanation for the diminished active range of motion found in our study [13,55].

Grip strength and key pinch strength of the injured side compared to the uninjured side seemed to be affected by PA. However, when correcting for dominance with the 10% rule, this statistically significant difference resides [36]. This finding supports literature emphasizing that grip strength is not a determinant of wrist function alone, but merely a reflection of overall muscle strength and condition of a chain of muscles in the upper limb [56]. We do believe that measurement of differences in grip strength between injured and uninjured side are relevant when determining follow-up outcomes of patients who sustained a DRF. Minimal detectable change (MDC) is defined as the smallest amount of change between two measurements that indicates a real change in measurement and not being a change due to measurement error [57]. This is a statistical measurement and does not take into account change as experienced by patients. Minimal clinically important difference (MCID) is the smallest change in a measurement that a patient would notice [57]. For grip strength MDC has been reported to be 6.5 kg and MCID 19.5% or 6.5 kg in patients 1 year following surgery for DRFs [58]. This suggests that the grip strength measurements between patients with and without PA presented in our study after a median follow up duration of 5.2 years are not noticeable for patients and therefore are possibly not clinically relevant. However, since PA is a chronic, progressive disorder, grip strength differences may become clinically relevant after a longer follow-up time. Further research is needed to provide more insight in this issue.

Patient reported outcomes

Pain did not differ statistically significant between patients with or without PA suggesting that pain may not be the main problem non-osteoporotic patients are facing following a DRF. In patients suffering from hand osteoarthritis pain intensity does not correlate strongly with radiographic classification [59]. The fact that the level of pain was similar in both groups might be explained by the relatively short follow-up period. However, the follow up duration was long enough to show a significantly decreased active range of motion in patients with PA compared to patients without PA. This suggests that evaluation of young patients with DRFs should not only be guided by pain but also by other domains.

Another interesting finding of the application of the different PROs was that performance of activities in daily life and work, as measured by the DASH and PRWE, questionnaires specifically designed for upper extremity functioning, was similar in patients with PA compared to those without PA. In contrast, general functioning, esthetics and satisfaction as measured by the MHQ subscales were statistically significant lower in patients with PA, as was the subscale physical functioning in the SF-36 and the total MHQ score. For future research these findings imply that other dimensions, different from those measured by the commonly used PRWE and DASH should be evaluated when measuring consequences of PA in patients with DRFs. MDC and MCID have been described to be respectively 7.7 and 17.3 for PRWE and 9.3 and 13.8 points for DASH [60]. For the MHQ none of the domains were reported to be discriminative after 3 years following volar plate fixation for DRFs, but for patients with carpal tunnel syndrome, MCIDs of 23, 13 and 8 were identified for the pain, function and work domains, respectively [61]. This suggests that the difference reported in this study in general function domain between patients with and without PA (10.0, p=.018) might not be relevant for patients. However, the study by Shauver *et al.* described 12 points difference on the satisfaction domain to differentiate between satisfied and unsatisfied patients. Therefore, the difference between patients with and without PA regarding the satisfaction domain (16.7, p=.044) might be clinically relevant. Unfortunately, no MDC or MCID have been described for the domains of the SF-36. It is surprising that the more subjective domains such as esthetics and satisfaction were statistically significant associated with PA and not the domains reporting on pain and (daily) functioning. The impact of PA for patients following DRFs in everyday life, while there is limited aROM, does not seem to be significant. However patients with PA are less satisfied. Further research should clarify the specific reasons for dissatisfaction.

Waljee *et al.* recently described a core set of domains that should be reported in order to get insight into outcomes after a DRF for clinical or research purposes: performance, PROs, pain, complications and radiographs [62]. Domains found in our study to be statistically significant different between participants with and without PA such as satisfaction and esthetics, are however lacking in this core set. To report about patient satisfaction is becoming increasingly important, since in modern medicine patient-centered health care is emphasized. Decision making in healthcare has shifted from a paternalistic model to informed decision-making and shared decision-making. There is evidence suggesting that shared decision-making does facilitate positive health outcomes and improves satisfaction [63]. In the future, it might be beneficial to further explore which elements of Waljee's proposed core set are relevant in the clinical follow up of non-osteoporotic patients following DRFs [62,64]. With regard to the PROs, we recommend the use of the MHQ subscales in clinical practice and post-injury DRF research, as this instrument seems to distinguish between patients with or without PA in the univariate analyses.

In literature, the few studies reporting on associations between CROs and PROs following DRFs describe these results at short-term follow up [65-68]. Chung *et al.* use two questions of the MHQ subscale satisfaction regarding range of motion and grip strength to determine cut-off points for satisfaction 3 month following a DRF. Optimal cut-points to distinguish satisfaction from dissatisfaction were met when patients recovered 65% of their grip strength and 95% of the wrist arc of motion [65]. Shauver *et al.* describe linear regression analyses revealing that 3 months following a DRF, patient's education, income, age at time of surgery and all measured outcome variables (grip strength difference, pinch strength difference, flexion, extension, active arc of motion, ulnar deviation, radial deviation, pronation, supination) accounted for 37% of the explained variance in total MHQ score [66]. Souer *et al.* describe a model where independent predictors pain ($F=61.16$, $p<.001$) and forearm rotation ($F=27.39$, $p<.001$) account for 71% of the explained variance of the DASH at a median follow-up of 6 months [68]. Our results support the finding that especially active range of motion is an important determinant of PROs. Type of treatment and AO/OTA fracture type did not seem to influence PROs. In addition, the influence of predicting factors seems to become less prominent with a longer follow-up duration as the explained variance in our study was lower than the earlier mentioned studies [66,68]. Future research should be aimed at determining a complete overview of factors influencing PROs following DRFs in non-osteoporotic patients at early, but also at longer follow-up period. From our study, we conclude that the development of PA impacts active range of motion. Patients perceive diminished general functioning and satisfaction following PA and diminished active range of motion. This insight could direct rehabilitation strategies and can be used to counsel these patients on expected outcome.

Our results reporting 10% change of occupation following a DRF are likely to be of major interest for patients. No statistically significant association with PA was found. Although all patients reported to have changed occupation because of the injury, this percentage might be a normal change of occupation in this population. It is striking however that all patients changed to a physically less demanding occupation and change of occupation occurred more often in physically demanding jobs. This suggests that patients more often need to adapt their working environment following a DRF when having a physically demanding occupation.

Strengths and weaknesses

Where most studies report on osteoporotic patients, sometimes combined with non-osteoporotic patients, we report on a young non-osteoporotic population who sustained a DRF 4-11 years ago. As such, we contribute to the knowledge PA and its association with radiological measurements, CROs and PROs in young patients. In addition, we have used measurements of the uninjured wrist as control when calculating the percentage of grip strength. Large variations between patients are accounted for in this way. The active range of motion and grip strength measurements were performed by one hand therapist for consistency. Measurements were performed in a fixed sequence. As a consequence however, fatigue effects may have influenced our results. In future research, a random sequence of measurements should be considered. Intraobserver and interobserver variability of radiological measurements and AO/OTA fracture classifications of DRFs on radiographs is known to be moderate [28,69] To eliminate interobserver variability, all measurements on radiographs were performed by one specialized radiologist. It has to be acknowledged that, although all radiographs have been performed according to protocol, measurement accuracy can be influenced by the quality of the radiograph taken and computed tomography could be more sensitive. The patients in our study did not have radiographic measurements out of normal ranges as described in literature [30-35]. Still, a prevalence of 32% PA at a relatively short follow up duration of 5 years is a substantial portion and is likely to progress with longer follow up duration. Our response rate was low, presumably because this population is young and has moved for study or work purposes and therefore many current addresses could not be retrieved. The included number of 73 patients might be insufficient to draw firm conclusions. However, in most studies describing populations after DRF the number of patients included in this study is not exceeded [10,68,75]. Moreover those studies do not report response rates [4,19,47,49]. Our results contribute to the knowledge on how to improve outcome and diminish PA in the future. However, studies with longer follow up duration are mandatory to gain more insight in the influence of progressed PA on outcome.

Conclusions

Non-osteoporotic patients had a considerably high prevalence of PA following DRFs, despite relatively short follow-up time. Correction of radial length should be performed as precise as possible, as overcorrection may induce PA. PA is associated with diminished flexion/extension and ulnar/radial deviation, irrespective of AO/OTA fracture type. Grip strength seems to be merely a determinant of strength and condition of the complete upper arm, as radiological measurements and PA does not seem to influence it. Non-osteoporotic patients following DRFs perceived diminished general functioning and dissatisfaction, which was impacted by the diminished active range of motion. Pain or impaired general health status were not reported. The PRO MHQ might be a valuable evaluation tool in this patient group. Change of occupation following DRFs should have attention in further research.

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CHAPTER 4

The evolution of radiological measurements and the association with clinician and patient reported outcome following distal radius fractures in non-osteoporotic patients: what is clinically relevant?

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ABSTRACT

Introduction. Recent literature puts normal ranges for radiological measurements following distal radius fractures (DRFs) in perspective by reporting on considerable error magnitudes. When reporting on clinician and patient reported outcomes (CROs and PROs), minimal important change (MIC) depicts the smallest change in a measurement that a patient would perceive as important which seems clinically more relevant than reporting statistical significance. Aims of this study were to determine 1) radiological measurement changes over time and report on clinical relevance of these changes, 2) report on clinical relevance of CROs and PROs and 3) to analyze associations between radiological measurements and CROs and PROs following DRFs in young non-osteoporotic patients.

Methods. Non-osteoporotic patients following a DRF were selected. Radiographs of both wrists were obtained at baseline, at 6 weeks and at follow-up. Radiological measurements consisted of ulnar variance, radial length, radial inclination, dorsal tilt, distal radio-ulnar joint width, scapholunate distance, step-off and gap. Active range of motion and grip strength measurements were performed and all patients filled in 4 questionnaires to assess pain, upper extremity functioning, and health status.

Results. Seventy-three patients (32 women, 41 men) with a mean age of 33.5 (SD 9.2) years at the time of injury were included. Median follow up was 62 months (IQR 53.0-84.5). Several radiological measurements evolved statistically significantly over time, however none exceeded measurement errors. Flexion/extension, ulnar/radial deviation and pro/supination were all diminished compared to the uninjured wrist (mean differences 11.2° (SD 12.6°), 6.9° (SD 9.9°) and 5.3° (SD 11.0°), respectively) as was grip strength (mean difference 2.6 kg (SD 6.0). Flexion/extension difference of injured compared to uninjured wrist exceeded MIC, while grip strength difference did not. When comparing patients with DRFs to healthy controls, only the differences on Patient Reported Wrist Evaluation (PRWE) subscales 'pain', 'function' and total scores did exceed MIC (8, 10 and 13 points respectively). Associations between radiological measurements and outcomes were found for step-off and diminished flexion/extension (regression coefficient -36.8, 95% CI -62.6; -11.1, p=.006), radial/ulnar deviation (regression coefficient -17.9, 95% CI 56.2; 61.7, p=.013) and ShortForm-36 'mental component score' (regression coefficient -15.4, standard error 5.5, p<.001). Shorter radial length was significantly associated with worse outcomes on all grip strength measurements. .

Conclusions. Radiological measurements following DRFs seem to evolve over time. However, changes were small and seem to be due to measurement error and might not yield clinically relevant changes. Range of motion, in particular flexion/extension, was clinically relevantly diminished, whereas grip strength was not impaired. PRO as reported with the PRWE was clinically relevant diminished. Residual articular incongruency seems to influence range of motion, where shortening of the radius influences grip strength. The association between residual articular incongruency and patient reported outcomes needs further atttention.

INTRODUCTION

Associations of radiological measurements with outcomes in young non-osteoporotic patients who sustained a distal radius fracture (DRF) have been described in a limited number of studies [1-3]. Radiological measurements that have mostly been used to describe the anatomy of the distal radius following a fracture are ulnar variance, radial length, radial inclination and dorsal angulation [4-9]. Normal ranges for radiological measurements have previously been described [4-9]. Recent literature puts these measurements in perspective by reporting on questionable intra- and interrater reliability and considerable error magnitudes of radiological measurements following DRFs [10]. In addition, since DRFs in young non-osteoporotic patients usually result from high energy trauma, these injuries often have intra-articular involvement [11]. This can result in residual articular incongruence, which is usually described in step-offs and gaps [12-17]. Error magnitudes of residual gaps and/or steps have been reported to be within 1-2mm [10]. As intra- and interobserver reliability of measuring residual gap and step were reported to be moderate to poor, it has been questioned if these radiographic measurements should be used as criteria for guiding treatment to be conservative or surgical [10,18]. Intercarpal ligamentous injuries, radiologically reflected in the distance between scaphoid and lunate (SL distance) and distal radio-ulnar joint (DRUJ) instability are also associated with DRFs and might influence outcome [11,19,20].

To interpret change scores of clinician reported outcomes (CROs: range of motion or grip strength), and patient reported outcomes (PROs: questionnaires) two benchmarks are required: the smallest detectable change (SDC) and the minimal important change (MIC), which the Consensus-based Standards for the development of Measurement Instruments (COSMIN) group defines as respectively 'the smallest change that can be detected by the instrument, beyond measurement error' and 'the smallest change in construct to be measured which patients perceive as important [21-23]. Most literature reports on SDC when reporting on outcomes following DRFs. This is a statistical measurement and does not take into account change as experienced by patients. Clinically more relevant is the MIC, which is the smallest change in an outcome measurement that a patient would perceive as important [21-24]. If the value of the MIC is less than that of the SDC, the MIC is within the limit of measurement errors or change [25,26]. Therefore, the MIC represents true clinical change when the value of the MIC is more than that of the SDC. The MIC threshold is very important in daily practice, where clinicians can compare at a patients' individual level, the current and previous values of outcome measures of interest. MICs regarding outcomes following DRFs have been reported scarcely on CROs [27,28] and PROs [29-31].

The association between radiological measurements and CROs, such as active range of motion (aROM) and grip strength measurements, remains unclear [1,8,12,32-39]. The association between radiological parameters and PROs presents conflicting results regarding patients of osteoporotic ages [12,33,34,40]. However, in young patients malalignment and ligamentous injury following DRFs is significantly more often associated with poorer CROs and PROs than in patients over 60 years of age [2,3]. We hypothesize that non-osteoporotic patients have higher demands of their wrist, because of an active working life and therefore might experience more impact of diminished function in daily life.

Summarizing existing literature, there seems to be a need for better understanding of changes in radiological measurements, their relation with outcomes and clinical relevancy of both radiological measurements and outcomes in young non-osteoporotic patients who sustained a DRF. Therefore, the aims of this study were to 1) analyze radiological measurement changes over time and report on their clinical relevance by comparing results to magnitude error, 2) report on clinical relevance of CROs and PROs following DRFs in young non-osteoporotic patients by comparing results with MICs as reported in literature and 3) to analyze associations between radiological measurements and CROs and PROs.

METHODS

All patients with a DRF who presented at a level II traumacenter between January 2005 and January 2011 and who were considered to be in a non-osteoporotic age range (men 18-50 years, women 18-40 years at the time of the injury) were retrieved from a local database. The age criteria were chosen to exclude patients with pre-existent osteoporosis [41-43]. Additional exclusion criteria were fractures treated after the 7th day following injury, open fractures, pre-existing osteoarthritis or risk factors for early osteoporosis (steroid use, alcohol abuse or early menopause), because outcomes in patients with these risk factors might not be representative for non-osteoporotic patients. The study was approved by the Medical Ethics Committee (NL41587.099.13) and registered at the Dutch Trial Registration (TC 4002). Patients were invited to pay a single visit to the hospital for functional measurements and radiographs of both wrists. Before entering the study, participants signed an informed consent form.

Radiological measurements

Radiographs were retrieved before treatment, immediately after intervention (closed reduction or surgical treatment), at 6 weeks following injury and at the participants' visit at follow up. For this study, baseline radiographs were defined as the accepted position of the DRF (either not needing reduction or following intervention) within 7 days following injury. At the time of the participants' visit, lateral (Lundy) and posteroanterior (PA) wrist radiographs were made of both wrists. All radiographs (baseline, 6 weeks and at follow up) were evaluated by a single radiologist specialized in musculoskeletal disorders with a special interest in hand and wrist anatomy.

Radiological parameters were measured according to the technique described by Kreder *et al.*; ulnar variance, radial length, radial inclination and dorsal angulation and step-off and gap (Figure 1) [18,44]. In addition, the scapholunate distance (SL distance) [45,46] and the distal radio-ulnar joint (DRUJ) space were measured [47,48] (Figure 1). Normal ranges and error magnitudes for radiological factors have previously been described and are depicted in Table 1.

To correct for anatomical variation between patients, radiographs of the uninjured wrist were obtained at follow up and used as a reference to interpret measurements of the injured wrist at baseline, at 6 weeks and at follow up.

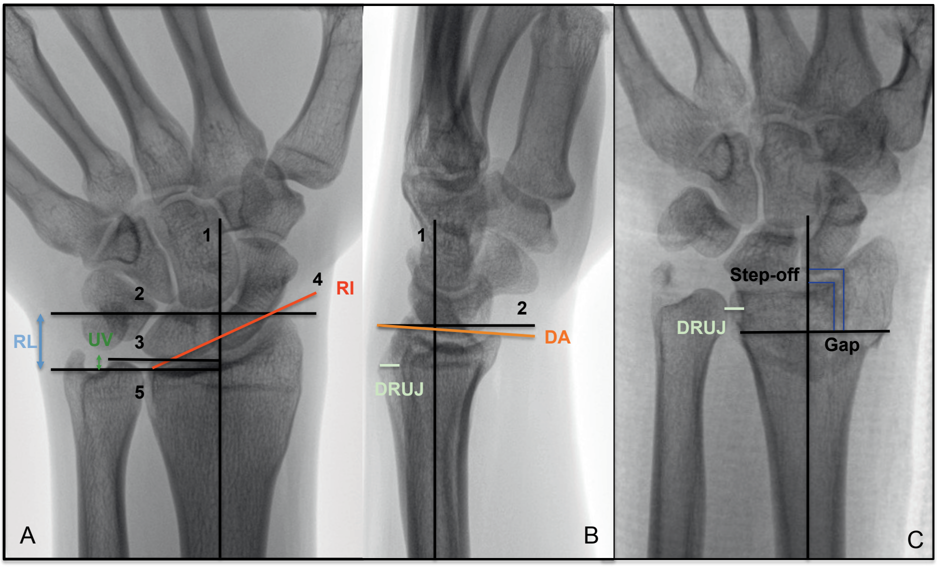

Figure 1. (A) Posteroanterior measurement guidelines: (1) The center of the radial shaft is determined at 3cm and 5cm below the mid-region of the proximal lunate articular surface. This line represents the central axis of the radius. (2) A line perpendicular to the central long axis of the radius is drawn at the level of the most distal aspect of the radial articular surface. (3) A line perpendicular to the central long axis of the radius is drawn at the level of the ulnar margin of the distal radial articular surface. (4) The radial and ulnar margins of the distal radial articular surface are connected. (5) A line perpendicular to the central long axis of the radius is drawn at the level of the distal ulnar articular surface. (B) Lateral measurement guidelines: (1) The center of the radial shaft is determined at 3 cm and 5 cm below the mid-region of the proximal lunate articular surface. This line represents the central long axis of the radius. (2) A line perpendicular to the central long axis of the radius is drawn at a convenient level. (3) The dorsal and anterior margins of the distal radial articular surface are connected. (C) Step-off and gap measurement. (1) Step-off at the articular surface of the distal radius was measured parallel to the central long axis of the radius by drawing perpendicular lines from the most distal margin of each side of the articular incongruence. (2) Gap deformity was measured along a perpendicular line to the central long axis of the radius. UV=ulnar variation, RL=radial length, RI=radial inclination, DT=dorsal tilt. SL=scapholunate ligament, DRUJ=distal radioulnar joint

Clinician reported outcomes

At the visit to the hospital at follow up, a single hand therapist recorded all clinician reported outcomes (CROs): active range of motion (aROM) and strength measurements. The participants were positioned sitting at a table, with hips and knees flexed in 90 degrees. Elbows were positioned on the table and flexed in 90 degrees with wrists in neutral position. The aROM of flexion/extension, ulnar/radial deviation and supination/pronation was measured using a digital protractor of Biometrics LTD and computed using E-Link® software. The aROM was presented in degrees. Grip strength, sustained grip strength and key pinch strength were measured using a digital Jamar dynamometer using Biometrics LTD and E-Link® software and presented in kilograms and as percentage of the uninjured hand. Grip strength and key pinch strength were presented in kilograms, and were derived from the maximum peak strength sustained during at least 2 seconds. The mean of three performances was calculated. For assessing sustained grip strength, patients were asked to grip as hard as they could using the dynamometer during a 30 second period. Sustained grip strength is the average grip strength in kilograms, computed over the last 18 seconds of this 30-second period. For people with rightsided dominance it is known that the right hand has 10% more grip strength in comparison to the left hand [49]. This is not the case when people are left sided dominant or ambidexter; grip strength in both hands is similar. Therefore, correction for dominance with the 10% rule was performed for grip strength measurements in individuals with right sided dominancy. First, all aROM measurements were recorded and subsequently grip strength measurements were assessed. Measurements were performed for both wrists. In addition, reference values for CROs in a healthy population (N=22, median age 48.5 years, IQR 39.5; 64.3) were derived from a previous published paper by our research group (Table 1) [50]. The SDCs en MICs as reported in literature for flexion/extension and grip strength are reported in Table 1 [27,28].

Patient reported outcomes

All patients completed 4 questionnaires involving pain scores, specific upper extremity functioning, and health status. Reference values for PROs in a healthy population were derived from the earlier mentioned 22 healthy controls (Table 1) [50].

The Disability of Arm, Shoulder and Hand (DASH) Questionnaire is a 30-item self-report measure assessing physical functioning and symptoms of the upper limb. DASH-scores range from 0 to 100 (higher scores indicate worse function). The DASH has a good validity, reliability and responsiveness in upper extremity disability assessment [51,52]. MIC of the DASH questionnaire has been described to be 10.83 points and SDC 10.81 points in 255 patients following upper limb musculoskeletal disorders with a mean age of 49 years and short follow up duration (Table 1) [29].

The Patient Rated Wrist Evaluation (PRWE) is a 15-item questionnaire divided into two subscales: pain (5 items) and function (10 items). The PRWE was developed to assess pain and functioning in patients with DRFs [53]. The pain items were selected to represent the total spectrum of frequency and intensity. The function items were selected to represent a range of physical activities that require different ranges of motions or muscle strength capabilities. For both subscales the maximum score is 50 (most disability) and the minimum score is 0 (no disability). Although these subscales have been reported frequently in literature, it has been suggested that the PRWE measures a single dimensional trait, and a single (sum) score should be used [54]. The questionnaire has a good validity for symptoms and function of the wrist [55]. For the PRWE following DRFs in 102 patients with mean age of 59 years, MIC has been determined at 11.5 points, while SDC was achieved at 11.0 points (table 1) [31].

Table 1. Reference values, error magnitudes, SDCs and MICs for radiological measurements, CROs and PROs

Radiological measurements	**Normal ranges**	**Error magnitudes** [10]	
Ulnar variance (mm)	-4- 2 [4,5]	2-4	
Radial length (mm)	8-17 [5]	4-6	
Radial inclination (°)	16-29 [6,7]	6-8	
Dorsal angulation (°)	0-22 [8,9]	6-8	
SL distance (mm)	< 2.0 [46]		
DRUJ distance (mm)	Related to uninjured wrist [47,48]		
Step-off (mm)	NA	1-2	
Gap (mm)	NA	1-2	
CROs	**Mean (SD)** [50]	**SDC**	**MIC**
Range of motion (°)			
Flexion/extension	150 (20)	4.3-5.0	5.0-7.1 [27]
Ulnar/radial deviation	61 (12)		
Supination/pronation	164 (14)		
Grip strength measurements (kg)			
Grip strength	45.1 (14.3)	6.5	6.5 [28]
Sustained grip strength	29.6 (10.6)		
Key pinch strength	9.0 (2.4)		
PROs	**Mean (SD)** [50]	**SDC**	**MIC**
DASH	3 (6)	10.8	10.8 [29]
PRWE			
Pain	1 (2)	6.5	1.5 [31]
Function	0 (1)	4.5	10
Total	1 (3)	11.0	11.5

SDC=smallest detectable change, MIC=minimal important change, CROs=clinician reported outcomes, PROs=patient reported outcomes, DASH=Disability of Arm, Shoulder and Hand questionnaire, PRWE=Patient Reported Wrist Evaluation, MHQ=Michigan Hand Questionnaire, SF-36=Short Form36

The Michigan Hand Outcomes Questionnaire (MHQ) assesses hand outcomes that are of importance to patients and specifically for the impaired hand (left and right separately) and includes 6 subscales; general function, activities of general life, work, pain, esthetics and satisfaction. The subscale score is the sum of the outcome of each question and ranges from 0 to 100. A higher score on the pain subscale indicates less pain. For the other five subscales and the total score higher scores imply a better function. The MHQ compares favourably with other PROs regarding upper extremity in the area of test-retest reliability, validity and responsiveness. In addition it has high internal consistence[56]. The strength of the MHQ is its multidimensional construct in measuring symptoms, function, aesthetics and satisfaction [56]. It has been reported that no discriminative ability is present as captured in MIC for the MHQ following DRFs, because of the ceiling effect with high scores at 3 months follow up and only a mean change of 10 points (mean score 3 months 78, mean score 12 months 89) [30].

The Short Form-36 (SF-36) is developed to survey overall health status [57]. It contains 36 questions to assess limitations in (1) physical function, (2) role function, (3) social function, (4) bodily pain, (5) general mental health, (6) limitations in role function due to emotional problems, (7) vitality and (8) general health perception. Scale scores range from 0 to 100 with higher scores indicating a better health status. Scale scores can be used to calculate a physical and a mental component summary score [57]. Validity of this questionnaire is sufficient for groups reporting varying extents of illness-health [58]. To our knowledge, no SDC or MIC values regarding the SF-36 have been published.

Statistical analysis

Continuous data were presented as means (SD) or as median (IQR) if no normal distribution of the data was present. T-tests were performed when analyzing continuous variables if a normal distribution was found. If continuous data did not have a normal distribution, Mann Whitney U tests were applied. Explanatory variables were included in the multivariable regression analysis when the *p*-value was ≤ 0.2 in the univariable regression analysis. Multivariable linear regression analysis, using backward stepwise selection (until all *p*-values were ≤ 0.2 to avoid excluding important risk factors) was performed analyzing radiological measurements as explanatory variables and CROs and PROs as dependent variables. Level of significance was set at $p \leq .05$. All statistical analyses were performed using IBM SPSS, version 22.

RESULTS

A total of 433 patients fulfilled the inclusion criteria and received an invitation to participate in the study. A notification of changed home address was received from 43 participants of whom current addresses could not be retrieved. From 306 patients, no response was received. Eighty-four patients responded of which seventy-three patients (32 women, 41 men) with a mean age of 33.5 (SD 9.2) years at the time of the injury, consented for participation after a median follow up of 62.0 months (IQR 53.0-84.5) (Table 2).

Table 2. Patient characteristics

		Total population (N=73)
Age at time of the injury (years)	Mean (SD)	33.5 (9.2)
Follow up (months)	Median (IQR)	62.0 (53.0;84.5)
		N (%)
Gender		
Male		41 (56.2)
Female		32 (43.8)
Energy trauma		
Low energy		20 (27.4)
High energy		45 (61.6)
Unknown		8 (11.0)
AO/OTA Classification		
A		14 (19.2)
B		30 (41.1)
C		29 (39.7)
Dominant hand injured		37 (50.7)
Left sided dominancy		2 (5.4)
Right sided dominancy		30 (81.1)
Ambidexter		5 (13.5)
Treatment		
Cast		33 (45.2)
Closed reduction/cast		12 (16.4)
Surgical		28 (38.4)

N=number of patients, SD=standard deviation, IQR=interquartile range, AO/OTA=Arbeitsgemeinschaft fur Osteosynthesefragen/Orthopedic Trauma Association classification

Radiological measurements

Baseline versus six weeks: DRUJ distance increased between baseline and 6 weeks post-injury (2.0 versus 2.4mm, p=.024). No other statistical significant differences between the measurements at baseline and 6 weeks were present and all measurement changes were within magnitude error (Table 3). SL distance at baseline and at 6 weeks exceeded the normal range of < 2.0mm by.2mm.

Table 3. Radiological measurements at baseline, 6 weeks and follow up. Results of paired samples T test

Radiological measurements	N	Baseline Mean (SD)	6 weeks Mean (SD)	Follow-up Mean (SD)
Ulnar variance (mm)	48	.4 (2.0)	.5 (1.8)	1.1 (1.9)
Radial length (mm)	47	12.2 (2.5)	12.8 (2.0)	12.7 (2.1)
Radial inclination (°)	49	23.7 (4.1)	24.4 (3.9)	25.2 (3.9)
Dorsal angulation (°)	46	-.6 (7.3)	-.2 (7.9)	-.2 (7.3)
SL distance (mm)	34	2.2 (.5)	2.2 (.4)	2.1 (.4)
DRUJ distance (mm)	43	2.0 (.7)	2.4 (.8)	2.4 (.8)
Step-off (mm)	37	.6 (1.2)	.5 (1.0)	.1 (.4)
Gap (mm)	43	1.7 (1.6)	1.7 (1.8)	.5 (1.4)

N=number of patients, SD= standard deviation, 95% CI=95% confidence interval, *=significant difference, SL=scapholunate ligament, DRUJ= distal radioulnar Joint, °=degrees, mm=millimeters

Table 4. Radiological measurements of the inured and uninjured wrist at follow-up. Results of paired samples T test

Radiological measurements	N	Follow up injured wrist Mean (SD)	Follow-up uninjured wrist Mean (SD)
Ulnar variance (mm)	73	.9 (1.8)	.4 (1.6)
Radial length (mm)	73	13.0 (2.1)	13.2 (2.1)
Radial inclination (°)	73	25.5 (3.6)	26.4 (3.8)
Dorsal angulation (°)	73	-1.3 (6.6)	-5.1 (4.1)
SL distance (mm)	45	2.1 (.4)	2.0 (.4)
DRUJ distance (mm)	72	2.4 (.8)	2.3 (.8)

N=number of patients, SD= standard deviation, 95% CI=95% confidence interval, *=significant difference, SL=scapholunate ligament, DRUJ= distal radioulnar Joint, °=degrees, mm=millimeter

Table 5. CROs derived from injured and uninjured wrist at follow-up. Results of paired samples T test

	Follow up injured wrist		Follow-up uninjured wrist	
aROM (N=73)	**Mean**	**SD**	**Mean**	**SD**
Flexion/extension (°)	141.3	18.2	152.5	13.4
Ulnar/radial deviation (°)	58.1	10.7	64.9	11.3
Pro/supination (°)	146.7	13.0	152.0	10.9
Grip strength (N=73)	**Mean**	**SD**	**Mean**	**SD**
Grip strength (kg)	43.5	13.2	46.1	12.7
Sustained grip strength (kg)	24.6	10.9	25.0	9.6
Key pinch strength (kg)	8.5	2.8	8.7	2.5

CROs=Clinician Reported Outcomes, N=number of patients, SD= standard deviation, 95% CI=95% confidence interval, *=significant difference, °=degrees, kg=kilogram, MCD=minimal detectable change, MCID=minimal clinically important difference

Baseline versus 6 weeks		6 weeks versus Follow-up	
Mean difference (SD)	*p*-value (95% CI of mean difference)	Mean difference (SD)	*p*-value (95% CI of mean difference)
-.7 (1.2)	-.7 (1.2)	-.7 (1.2)	<.001 (-1.1; -.4)*
-.7 (1.2)	.817 (-.6; .5)	.2 (1.3)	.897 (-3; .4)
.2 (1.3)	.113 (-1.4; .2)	-.9 (2.8)	.028 (-1.7; -.1)*
-.9 (2.8)	.288 (-2.1; .6)	.0 (5.2)	.978 (-1.5; 1.5)
.0 (5.2)	.627 (-2.1; 1.3)	.1 (.4)	.114 (-.0; .3)
.1 (.4)	.660 (-.2; .1)	-.0 (.7)	.843 (0.2; .2)
-.0 (.7)	.024 (-.6; -.0)*	.3 (.9)	.032 (.0; .7)*
.3 (.9)	.845 (-.3; .3)	1.0 (1.6)	.001 (.5; 1.6)*

Mean difference (SD)	Significance *p*-value (95% CI of mean difference)
.4 (1.9)	.063 (-.0; .9)
-.2 (2.1)	.318 (-.7; .2)
-.9 (4.2)	.079 (-1.9; -.1)
3.8 (6.5)	<.001 (2.3; 5.3)*
.1 (.5)	.099 (-.0; .3)
.1 (.7)	.224 (-0.1; .3)

Mean difference (SD)	Significance *p*-value (95% CI of mean difference)
-11.2 (12.6)	<.001* (-14.1; -8.2)
-6.9 (9.9)	<.001* (-9.2; -4.6)
-5.3 (11.0)	<.001* (-7.9; -2.8)
	***p*-value (95% CI of mean difference)**
-2.6 (6.0)	<.001* (-4.0;-1.2)
-.4 (6.4)	.574 (-1.9; 1.1)
-.1 (2.0)	.547 (-.6; .3)

Six weeks versus follow-up: Between 6 weeks and follow-up, ulnar variance and radial inclination increased (mean .4mm versus 1.12mm, p<.001, and 24.3° versus 25.2° , p=.028, respectively) (Table 3). In contrast, the step-offs and gaps diminished (step-off .4 versus .1mm, p=.032, gap 1.5 versus .1mm, p=.001) (Table 3). However, none of the measurement changes exceeded error magnitudes. SL distance at 6 weeks and follow-up exceeded the normal range of <2.0mm with respectively .2 and .1mm.

Injured versus uninjured wrist: When comparing the radiological measurements of the injured to the uninjured wrist at follow up, dorsal angulation was statistically significantly more pronounced in the injured wrist (-1.3° versus -5.1°, p<.001) (Table 4). This measurement change did not exceed the reported error magnitude of 6-8°.

Clinician reported outcomes

All aROM measurements of the injured wrist were statistically significantly lower in comparison to the uninjured wrist at follow up (Table 5). With regard to flexion/extension the difference of 11.2° exceeded the reported MIC of 5.0-7.1°.

Grip strength of the injured wrist was statistically significantly lower in comparison to the uninjured wrist at follow up (Table 5). The grip strength difference of 2.6 kg between the injured and uninjured wrist did not exceed the reported MIC of 6.5 kg.

Patient reported outcomes

When comparing PROs with outcomes as reported for healthy controls, the differences for PRWE subscales pain, function and total PRWE score all exceeded the reported MICs. The difference between DASH scores did not exceed the reported MIC of 10.83 (Table 6).

Associations between radiological measurements, CROs and PROs

Multivariable regression analyses revealed that step-off was statistically significantly associated with diminished flexion/extension as well as ulnar/radial deviation (Table 7). Multivariable analyses revealed that shorter radial length was associated with diminished grip strength measurements (Table 7) (See Appendix for univariable regression analyses regarding CROs).

Only SF-36 physical component score and mental component score were entered in the multivariable regression analyses (Table 8). SF-36 mental component score was associated with step-off (See Appendix for univariable regression analyses regarding PROs).

Table 6. PROs at follow up compared to measurements of healthy controls

PROs	All patients (N=73) Mean (SD)	Healthy controls [50] (N=22) Mean (SD)	Difference	MIC
DASH	9 (12)	3 (6)	6	10.8 [29]
PRWE				
Pain	9 (11)	1 (2)	8	1.5 [31]
Function	10 (15)	0 (1)	10	10
Total	14 (17)	1 (3)	13	11.5
MHQ	84 (16)	98 (3)	14	
SF-36				
Physical functioning	92 (12)	93 (15)	1	
Social functioning	90 (19)	95 (12)	5	
Role model physical problem	86 (28)	88 (30)	2	
Role model emotional problem	90 (27)	95 (21)	5	
Mental health	83 (13)	89 (11)	6	
Vitality	71 (18)	82 (15)	11	
Pain	81 (19)	90 (14)	9	
General health experience	73 (18)	78 (14)	5	
Health change	52 (20)	51 (14)	1	

N=number of patients, PROs=patient reported outcomes, DASH=Disability of Arm, Shoulder and Hand questionnaire, PRWE=Patient Reported Wrist Evaluation, MHQ=Michigan Hand Questionnaire, SF-36=Short Form-36, SDC=smallest detectable change, MIC=minimal important change

Table 7. Multivariable regression analyses of radiological measurements and CROs

Dependent	Explanatory variables	Regression coefficient (SE)	*p*-value	95% CI
Flexion/extension	Step-off	-36.8 (12.8)	.006*	-62.6;-11.1
	Constant	143.3 (2.5)	<.001*	138.3;148.4
Ulnar/radial deviation	Step-off	-17.9 (7.0)	.013*	-32.0;-3.9
	Constant	58.9 (1.4)	<.001*	56.2;61.7
Pro/supination	Constant	59.1 (1.6)	<.001*	55.8;62.5
Grip strength	Radial length	2.8 (.7)	<.001*	1.5;4.1
	Constant	7.2 (8.6)	.403	-9.9; 24.4
Sustained grip strength	Radial length	2.1 (.6)	<.001*	1.0;3.2
	Constant	-2.9 (7.2)	.681	-17.4;11.4
Key pinch strength	Radial length	.5 (.1)	<.001*	.2;.7
	Constant	2.4 (1.6)	.135	-.8;5.5

CROs=Clinician Reported Outcome, SE=standard error, 95% CI=95% confidence interval, *=significant difference

Table 8. Multivariable linear regression analysis for radiological measurements and PROs

Dependent	Explanatory variables	Regression coefficient (SE)	*p*-value	95% CI
SF 36 physical component	SL distance	-10.1 (5.3)	.063	-20.9; .6
	Constant	105.4 (11.6)	<.001*	82.2; 128.6
SF 36 mental component	Step-off	-15.4 (5.5)	.008*	-26.6; -4.2
	Constant	86.8 (2.0)	<.001*	82.8; 90.7

PROs=Patient Reported Outcomes , SF-36=Short Form 36, SE=standard error, 95% CI=95% confidence interval, *=significant difference, SL=scapholunate ligament

DISCUSSION

Multiple radiological measurements changed statistically significantly over time. However, none of the measurement changes exceeded reported magnitude errors. As such, clinical relevancy could not be revealed.

All aROM measurements were statistically significantly diminished in the injured wrist compared to the uninjured wrist. Since MIC is only reported for flexion/extension, this finding appeared to be clinically relevant. Although grip strength was statistically significantly lower in the injured wrist, the difference was not clinically relevant. The differences between patients with DRFs and healthy controls for PRWE subscales pain, function and total PRWE score all exceeded the reported MICs, suggesting a clinically relevant diminished score for non-osteoporotic patients following a DRF. Associations between radiological measurements and outcomes were found for step-off and diminished flexion/extension as well as ulnar/radial deviation and SF-36 mental component score. Radial length was associated with all grip strength measurements.

The evolution of radiological measurements in perspective

Ulnar variation, radial length, radial inclination and dorsal angulation were within normal ranges as presented in literature at all follow-up moments [4-9]. Neidenbach *et al.* stated that most changes of radiological measurements occur in the first 6 weeks following injury [34]. Although this seems to be logical, our study did not show many signs of radiological changes in the first 6 weeks following initial treatment after a DRF. Although these authors stated that no changes in radiological measurements occur between 6 weeks and 1 year follow-up, our study did suggest that ulnar variance and radial inclination increased and step-off and gaps diminished during 5 years following a DRF [34]. When ulnar variance and radial inclination increase, but radial length does not increase, a compression (and relative shortening) of the ulnar side of the distal radius must be present. Rikli and Regazzoni described this anatomical area in 1996 as the intermediate column [59,60]. It consists of the lunate facet and the sigmoid notch and is responsible for >50% of the axial compressive forces that are transmitted across the wrist during normal activity [61]. Brink and Rikli acknowledge the importance of the intermediate column and describe the volar and dorsal ‘key corner’ of the intermediate column. They state that control with reduction and stable fixation of this ‘key corner’ should be the first step of the operative strategy after a DRF, because insufficient treatment may result in carpal subluxation [60]. Our results suggest that the intermediate column is likely to be compressed after 6 weeks following a DRF, which may result in shortening. We agree with Brink and Rikli that care should be taken to pursue anatomical reduction and stable fixation of the intermediate column. However, when comparing the differences in measurements in our study to reported magnitude error by Watson *et al.*, all findings were within the 95% confidence interval of expected normal ranges [10]. This suggests that the evolution of these radiological measurements over time might be regarded as measurement error and might not yield a clinically relevant change.

SL distance in our study exceeded the normal value of <2.0mm with only 0.1-0.2 mm and was not statistically significantly different in comparison to measurements of the uninjured wrist [46]. In addition to proper physical examination, it has been reported that diagnosing concomitant ligamentous injury on static radiographs is challenging, as only Geissler type IV lesions are represented by a distance between scaphoid and lunate > 2mm due to a complete SL tear [19,46,62-64]. Prevalences up to 98% of associated ligamentous injury with DRFs, mostly SL ligament injuries, have been described [64,65]. Fortunately, most often these injuries do not need surgical repair when treating DRFs, because very rarely the SL injury significantly affects carpal stability and outcome [19,62]. We therefore hypothesize that the measurements regarding SL distance in our study do not represent ligamentous injury with significant impact on outcome.

DRUJ distance increased statistically significantly from 2.0 to 2.4mm between baseline and 6 weeks, but this distance did not differ significantly from the uninjured wrist. In literature it has been described that DRUJ instability is suspected when a difference is present between DRUJ distance on PA radiographs of the injured compared to the uninjured wrist. In addition, when on a lateral radiographs a distance is measured exceeding 4-5mm between the dorsal cortexes of the distal radius and ulna, this is also a suggestion for DRUJ instability [48]. We therefore conclude that in our study DRUJ instability was most likely not present.

Residual articular incongruence in perspective

Surprisingly, our results showed that step-off and gap diminished significantly between 6 weeks and follow-up, although these differences were within earlier mentioned magnitude error [10]. Conflicting results regarding reliability of measuring gaps and step-offs following distal radius fractures have been reported. It has been reported that observers, independent of skill level, may measure step-off and gaps accurately to .62± 53mm (95% CI .59-.65). [66] Intraclass correlation coefficient scores showed 'substantial' (.78) to 'almost perfect' (.81) inter- and intraobserver agreement [66]. In contrast, other studies reported low intra- and inter-reliability ICC values [10,18]. Watson *et al.* showed that measurement error lies within 1-2 mm, indicating that clinicians cannot measure differences ≤ 1mm. They therefore questioned the reliability of using these radiographic measurements to guide treatment decisions regarding conservative or operative management [10]. To our knowledge, no literature on the decrease of articular incongruence over time in adult patients is available. Bone healing is a complex event that involves coordination of two complex forces: anabolism or tissue formation and catabolism or remodelling under influence of axial, translational and rotational forces [67,68]. Possibly remodelling processes have diminished the articular incongruence.

Outcomes in perspective

Flexion/extension seems to be a clinically relevant measurement in non-osteoporotic patients following DRFs, because our findings seemed to exceed MIC references [27]. As reported by our research group and others, it is well known that fractures healed with a step-off ≥ 2mm are associated with development of PA, which may affect CROs and PROs [12,13,15-17,32,69]. Multiple studies report on better CROs following plate fixation with better anatomical realignment of articular congruence in comparison to conservative treatment or external fixators [70-72]. Unfortunately, no MICs for ulnar/radial deviation and pro/supination are reported in literature. Therefore, further research is mandatory to determine MIC references to evaluate the clinical relevance of CROs. We conclude that patients with a DRF should be informed that lasting limitations in flexion/extension can be expected.

Although in our study a statistically significant difference in grip strength between the injured and uninjured wrist was found, this result did not exceed the reported MIC [28]. This suggests that no clinically relevant impact on grip strength is expected following DRFs. As such, grip strength seems to be merely a reflection of overall strength and the physical condition of a chain of muscles in the upper limb [73].

In our study, the MIC of the DASH was not exceeded, but MICs of PRWE subscales pain, function and total score were [29,31]. For the MHQ, no discriminative ability is present as captured in MIC following DRFs, because of the ceiling effect of the MHQ with high scores at 3 months follow up [30]. To our knowledge, no literature reported on MICs of the SF-36 following DRFs so far. However, seemingly substantial differences between patients with DRFs and healthy controls on subscales MHQ general function, work, pain, satisfaction as well as the total MHQ were found. In addition, for the SF-36 subscales vitality and pain this seemed also to be true. More knowledge on reference MICs regarding PROs is mandatory to put these differences in clinical perspective. It is known that outcomes as measured with PROs and assessed using MICs can differ significantly between certain injuries or disorders and can therefore not be extrapolated [56]. In addition, slight variation exists in the psychometric properties of PROs measuring outcomes of different injuries or disorders, which can hamper comparability [54,74,75]. Waljee *et al.* and Goldhahn *et al.* have proposed a core set of parameters including aROM, grip strength, the PROs PRWE, DASH, MHQ, and the Patient Reported Outcome Measurement Information System (PROMIS®) upper extremity item banks to be included when reporting in literature on DRFs to improve comparability [76,77]. We believe that reporting on aROM, grip strength and PROs with adequate MICs would improve interpretability of the clinical relevance of outcomes following DRFs in non-osteoporotic patients immensely.

Associations between radiological measurements and outcome in perspective

Step-offs were significantly associated with diminished flexion/extension and ulnar/radial deviation. Several authors reported on the association between articular incongruency following DRFs and the association with development of posttraumatic arthritis (PA) at longer follow up duration [12,14,78-80]. The development of PA is related to several causes, such as increased stress on the articular surface following overcorrection of radial length, radiocarpal instability caused by ligamentous injuries or articular incongruency [17,81,82].

Radial length seems to be important to correct surgically, because radial shortening may result in diminished grip strength. However, this decreased grip strength may not be clinically noticeable for a patient, because measurements did not exceed reported MICs [28]. Note that several reports have associated radial shortening with diminished ROM and diminished grip strength measurements [32,38,83-85]. In contrast, a few others did not find such associations [34,35]. Radial shortening may cause an increased pressure in the DRUJ and a shift in the centre of pressure within the sigmoid notch and can cause diminished ROM and grip strength [86-88].

Articular incongruence of ≥ 1mm may lead to lower SF-36 scores [14] as is supported by our study in which the SF-36 mental component score was significantly associated with residual step-off. Unfortunately no MICs are reported for the SF-36 and no sound conclusion can be drawn. It does illustrate the need for more knowledge on MICs following DRFs when reporting on outcome using PROs.

Strength and weaknesses

By reporting on a young non-osteoporotic population who sustained a DRF 4-11 years ago, we contribute to the knowledge on radiological measurements after a DRF and their associations with CROs and PROs. All CRO measurements have been performed by one hand therapist for consistency. To eliminate interobserver bias, all measurements on radiographs were assessed by one specialized radiologist. It has to be acknowledged that, although all radiographs have been taken according to protocol, measurement accuracy can be influenced by the quality of the radiographs. Our response rate was low, presumably because our population was young and moved for study or work purposes and therefore many current addresses could not be retrieved. The included number of 73 patients might be insufficient to draw firm conclusions. However, in most studies describing populations after DRFs, the included number of patients did not exceed our cohort [11,71,89]. To our knowledge, no MIC values regarding the PROs MHQ and SF-36 have been reported yet. Therefore we have compared the results of our cohort to a healthy young non-osteoporotic cohort of 22 participants. Care should be taken when drawing conclusions regarding comparisons with this healthy cohort, because the sample size is minimal. In addition, lack of consensus regarding the best methodology to determine the MIC exists. There are two main approaches; anchor-based methods in which an external criterion is used to define an important change (often patient-based judgement) and distribution-based methods, which use statistical measures as a value for MIC [75]. This could result in large variations in MIC values for CROs and PROs reported in literature [75]. Care should be taken to interpret MIC values and consensus should be reached on the preferred MIC methodology.

Conclusions

Radiological measurements following DRFs seem to evolve over time. However, changes were small and might be due to measurement error and might not yield clinically relevant changes. Range of motion, in particular flexion/extension, was clinically relevantly diminished in non-osteoporotic patients following a DRF. Grip strength was not clinically noticeably impaired. Residual articular incongruency seemed to influence range of motion. The association between residual step-off and mental health needs further atttention. Further research on MIC is mandatory, to enhance interpretation of clinically relevant outcomes after a DRF.

APPENDIX

Table 9. Univariable regression analyses of radiological measurements and CROs

	aROM		
Radiological factors	**Flexion/extension**		
	B	**95% CI**	***p*-value**
Ulnar variance (mm)	.050	-2.2;2.4	.966
Radial length (mm)	-.034	-2.0;2.0	.973
Radial inclination (°)	.856	-.3;2.0	.153*
Dorsal angulation (°)	.078	-.6;.7	.812
SL distance (mm)	-5.853	-17.0;5.3	.296
DRUJ distance (mm)	-.051	-5.6;5.4	.985
Step-off (mm)	-12.9	-27.9;2.2	.092*
Gap (mm)	-5.154	-9.3;-1.0	.016*
	Strength measurements		
Radiological factors	**Grip strength**		
	B	**95% CI**	***p*-value**
Ulnar variance (mm)	.7	-1.0;2.4	.384
Radial length (mm)	2.8	1.5;4.1	<.001*
Radial inclination (°)	.4	-1.5;1.3	.361
Dorsal angulation (°)	.2	-.3;.6	.486
SL distance (mm)	5.0	-4.1;14.2	.273
DRUJ distance (mm)	2.0	-2.0;5.9	.324
Step-off (mm)	.2	-9.8;10.2	.968
Gap (mm)	1.2	-1.8;4.2	.440

aROM=active range of motion, B=regression coefficient, 95% CI=95% confidence interval, *=significant difference, SL=scapholunate ligament, DRUJ=distal radioulnar joint, mm=millimeter

Ulnar/radial deviation			Pro/supination		
B	95% CI	*p*-value	B	95% CI	*p*-value
-.714	-2.1;.6	.298	-.523	-2.2;1.1	.532
-.459	-1.6;.7	.440	-.720	-2.1;.7	.318
-.052	-.8;.7	.882	-.250	-1.1;.6	.562
.167	-.3;.6	.475	.167	-.3;.6	.475
4.281	-3.2;11.7	.254	10.490	2.2;18.8	.014*
-3.468	-6.6;-.3	.030*	.130	-3.8;4.1	.947
-6.759	-14.6;1.1	.089*	1.105	-8.4;10.6	.816
-3.070	-5.3;-.8	.008*	-5.149	-7.8;-2.5	<.001*

Sustained grip strength			Key pinch strength		
B	95% CI	*p*-value	B	95% CI	*p*-value
.4	-.9;1.8	.549	-.1	-.4;.3	.768
2.1	1.0;3.2	<.001*	.5	.2;.7	<.001*
.3	-.4;1.0	.458	.1	-.1;.2	.266
.1	-.3;.5	.767	.0	-.1;.1	.362
2.1	-5.9;10.2	.600	.5	-1.1;2.0	.530
1.7	-1.4;5.1	.279	-.1	-.8;.6	.783
-.5	-8.6;7.6	.903	-1.2	-3.1;.7	.218
.5	-1.9;2.8	.711	-.2	-.8;.4	.563

Table 10. Univariable regression analyses for radiological measurements and PROs

	PROs								
Radiological factors	**DASH**			**PRWE**					
				Pain			***Function***		
	B	**95% CI**	***p***	**B**	**95% CI**	***p***	**B**	**95% CI**	***p***
Ulnar variance (mm)	.9	-.6;2.3	.238	1.1	-.3;2.4	.113*	1.8	-.1;3.6	.060*
Radial length (mm)	-.2	-1.5; 1.1	.760	-.1	-1.2;1.1	.914	-.8	-2.4;.8	.339
Radial inclination (°)	.2	-.6;1.0	.596	-.1	-.8;.6	.807	-.2	-1.2;.7	.624
Dorsal angulation (°)	.0	-.4;.4	.943	-.1	-.5;.3	.668	.1	-.4;.6	.680
SL distance (mm)	.9	-6.6; 8.4	.809	2.3	-5.0;9.7	.528	1.8	-9.2; 12.9	.742
DRUJ distance (mm)	-.7	-4.2; 2.8	.686	.7	-2.5;3.9	.658	-2.4	-6.8;2.0	.280
Step-off (mm)	1.1	-8.8; 11.0	.817	.3	-8.7;9.2	.956	-1.3	-14.3; 11.8	.849
Gap (mm)	1.3	-1.6; 4.2	.376	.2	-2.5;2.8	.902	.8	-3.1;4.6	.699

PROs=Patient Reported Outcomes, DASH= Disability of Arm Shoulder Hand questionnaire, PRWE= Patient Rated Wrist Evaluation, MHQ= Michigan Hand outcomes Questionnaire, SF-36= Short Form 36, B=regression coefficient, 95% CI= 95% confidence interval, p=*p*-value, *=p<.200, SL=scapholunate ligament, DRUJ=distal radioulnar Joint, mm=millimeter

			MHQ			SF 36					
Total						*Physical component*			*Mental component*		
B	95% CI	*p*	B	95% CI	*p*	B	95% CI	*p*	B	95% CI	*p*
2.0	-.1;4.1	.068*	-.4	-2.4;1.7	.741	.3	-1.8;2.4	.781	1.3	-.7;3.3	.200*
-.5	-2.3;1.4	.625	1.1	-.7;2.8	.230	.1	-1.7;1.9	.933	.5	-1.3; 2.3	.597
-.2	-1.3;.9	.700	.3	-.7;1.3	.569	-.5	-1.6;.5	.327	-.3	-1.4;.8	.569
-.1	-.6;.6	.927	-.2	-.8;.4	.455	-.1	-.6;.5	.830	.1	-.5;.7	.773
3.2	-8.9; 15.4	.594	-4.7	-15.8; 6.5	.404	-10.1	-20.9; .6	.063*	-7.2	-17.2; 2.8	.155*
-.5	-5.6;4.6	.841	2.5	-2.2;7.3	.289	3.2	-1.6;8.0	.193*	2.4	-2.5; 7.2	.335
-.2	-14.8; 14.4	.977	-7.7	-21.6; 6.2	.272	-5.8	-19.1; 7.5	.383	-9.5	-22.1; 3.1	.138*
.6	-3.7;4.9	.784	-2.0	-6.1;2.1	.330	-.3	-4.2;3.5	.872	-.5	-4.2; 3.1	.772

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CHAPTER 5

Pain, impaired functioning, poor satisfaction and diminished health status eight years following perilunate (fracture) dislocations

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ABSTRACT

Introduction. Perilunate (fracture) dislocations are rare injuries and diminished clinician reported outcomes are reported. However, patient reported outcomes following these injuries are rarely described. The aim of this study was to investigate the long-term impact of perilunate (fracture) dislocations using a range of measures, including pain, function and quality of life.

Methods. This cross-sectional study was conducted from January 2016 until March 2016. Eleven patients who had suffered from perilunate (fracture) dislocations between August 1996 and January 2014 were matched on age and gender with 22 healthy controls. Functional outcome included range of motion and grip strength measurements. The Patient Reported Outcomes included: Patient Reported Wrist Evaluation, Disability of Arm, Shoulder and Hand questionnaire, Michigan Hand Questionnaire and the Short Form-36.

Results. The 11 patients that were included (9 males) had a median age at injury of 38 years (IQR 33; 54) and median follow up of 97 months (IQR 84-193). Flexion/extension (mean difference -60°, 95% CI -76, -43, p<.001) and ulnar/radial deviation (mean difference -28°, 95% CI -38, -18, p<.001) were significantly diminished in patients following perilunate (fracture) dislocations. Grip strength was not affected. The patients experienced significantly more pain as assessed on all pain subscales. Physical functioning was significantly worse in the group with perilunate (fracture) dislocations as assessed on all function subscales, except the PRWE function score and the subscale physical functioning of the Short Form-36. Satisfaction as measured with the Michigan Hand Questionnaire satisfaction subscale (mean difference -36, 95% CI -57, -16, p=.002) was also reported poorer. No difference was found regarding work participation.

Conclusions. A perilunate (fracture) dislocation has a significant impact on everyday life, as patients experience diminished range of motion, pain, diminished physical functioning, diminished satisfaction and report lower general health status than healthy controls. However, no consequences for work participation were found in this study. Level of evidence 3.

INTRODUCTION

Perilunate dislocations and perilunate fracture dislocations (PLD/PLFDs) are rare injuries of the wrist and comprise only 7% of all carpal injuries [1-5]. PLFDs occur more frequently than PLDs (ratio 2:1), in which the scaphoid bone is most often fractured. [6] Most PLD/PLFDs are seen following injury with high energy transmission. Twenty percent of all PLD/PLFDs are associated with polytrauma [7]. Regarding clinician reported outcomes (CROs), diminished range of motion of 59-82% and grip strength measurements ranging from 59-87% in comparison to the uninjured wrist were reported 6-months to 5 years following PLD/PLFDs [3,8-11]. In addition, poor patient reported outcomes (PROs) have been published in patients with PLD/PLFDs with Disability of Arm Shoulder Hand (DASH) scores ranging from 14-40 and Patient Rated Wrist Evaluation (PRWE) scores ranging from 13-41 [3,8-13]. Complicated PLD/PLFD is thought to result in even poorer outcomes due to extensive soft tissue damage [7]. Late identification of PLD/PLFDs ligament ruptures or accompanying fractures also lead to worse outcomes [2,7,14-16]. Bone necrosis and posttraumatic arthritis is known to develop following this injury [17]. Prevalence of posttraumatic arthritis following PLD/PLFDs of up to 56% has been reported 6 years post-injury [7]. The development of posttraumatic arthritis of the wrist increases with direct or indirect impact load on the joint, soft tissue contusion, joint dislocation and intra-articular fractures (most often scaphoid bone fractures) [18-20]. Posttraumatic arthritis can result in severe functional impairment with regard to range of motion and grip strength [18].

In order to treat and guide patients with PLD/PLFDs optimally, it is important to have knowledge on specific CRO measurements, such as grip strength and active range of motion, as well as PROs. Loss of grip strength, limited range of motion of the wrist and pain are common findings after PLD/PLFDs and lead to impaired functioning in daily life [13,15,16]. Impairment has been described to such extent that patients did not return to work or had to change to a less strenuous occupation [10]. In case of PLD/PLFDs, some studies reported on PROs [3,8-13]. The Cooney rating system or Mayo Wrist Score are often reported, which are aggregated scores of pain, functional status, range of motion and grip strength [4,13,21]. Although both systems are easy to use, they are not validated and the rating does not differentiate between functional outcome and PROs. There is a need for more insight in long term outcomes captured in functional outcomes and PROs in this working and mostly active population. We believe this may help to develop more targeted surgical and rehabilitation treatment strategies minimizing long-term consequences of this injury. Furthermore, information regarding pain, satisfaction, daily and general functioning is needed to inform patients on their long-term outcomes. However, these measures are scarcely reported in literature. Furthermore, results are most often not compared with matched controls, which could hamper the interpretation of the outcomes.

The purpose of this study was to gain better insight in the specific limitations in long-term functioning following PLD/PLFDs. The aims of this study were to assess CROs and PROs of patients following PLD/PLFDs and compare the outcomes with results of matched control patients.

METHODS

Study population

This cross-sectional study was performed at a level 1 traumacenter and was approved by the local medical ethics committee (METC NL52111.042.15). Patients and controls provided written informed consent before entering the study. All patients received an invitation for a single visit to the hospital and received a gift voucher and compensation for travel expenses after having participated in the study.

Hospital records of patients treated for a PLD/PLFD between August 1996 and January 2014 were retrieved. Patients who consented for participation were measured between January 2016 and March 2016. Inclusion criteria were: minimal follow up duration of 2 years, mental competence, living in the Netherlands and having sufficient control of the native language in order to answer the questionnaires. Exclusion criteria were: comorbidity that might influence the outcomes, such as neurological or rheumatic disorders influencing arm function. Since surgery is the advised treatment option for PLD/PLFD patients, those with contraindications for surgical treatment at the time of injury were excluded, because worse outcomes can be expected without surgical treatment [22]. The controls were individually matched on age (+/- approximately 2 years) and gender. Every PLD/PLFD patient was matched with two controls. Controls with different occupations and various educational levels were recruited among hospital personnel and acquaintances of the researchers.

Clinician reported outcomes

The CROs of the PLD/PLFD group were obtained by a certified hand therapist and CROs of the matched controls were obtained by one of the authors. For measurements of all CROs (range of motion and grip strength measurements) patients were positioned sitting positioned sitting at a table, with hips and knees flexed 90˚. In addition, elbows were positioned on the table and flexed in 90˚ with wrists in neutral position.

The flexion/extension, ulnar/radial deviation and supination/pronation range of motion were measured using a digital protractor of Biometrics LTD and E-Link® software and expressed in degrees and in percentage of the uninjured side.

Grip strength, sustained grip strength and key pinch strength were measured using a digital Jamar dynamometer and a pinch meter using Biometrics LTD and E-Link® software. Grip strength and key pinch strength were presented in kilograms and percentage of the uninjured side, and were derived from the maximum peak strength sustained during at least 2 seconds. The mean of three performances was presented. Grip strength of less than 75% compared to the uninjured side was considered as an adverse outcome [23]. For assessing sustained grip strength, patients were asked to grip as hard as they could using the dynamometer during a 30 second period. Sustained grip strength is the average grip strength in kilograms, computed over the last 18 seconds of this 30-second period. In all patients first the arcs of motion measurements, then grip strength measurements were performed, alternating between both hands.

Patient reported outcomes

PROs were measured using four questionnaires involving pain scores, health related quality of life, satisfaction and specific hand and wrist functioning.

DASH. The Disability of Arm, Shoulder and Hand questionnaire (DASH) measures upper extremity performance in 30 activities of daily living and two optional scales of 4 questions each measuring work and leisure time participation. Scores range from 0 to 100. A higher score indicates more disability or severity of complaints. DASH has a good validity for symptoms and function of the upper limb. [14] The Dutch version (DASH-DLV) has recently been validated and combines outcome measures such as pain, function or patient satisfaction in a unidimensional trait [24,25].

PRWE. The Patient Rated Wrist Evaluation questionnaire (PRWE) rates a patients' level of both wrist pain and disability. The pain subscale contains five questions, which are rated from 0 (no pain) to 10 (unbearable pain). The function subscale contains ten questions, which are divided into two sections concerning specific activities and usual activities. For each section the minimum score is 0 (no disability) and the maximum score is 50 (worst possible disability) [14]. The questionnaire has a good validity for symptoms and function of the wrist [26]. The translated version of the PRWE (PRWE-NL) has been validated and confirmatory factor analysis revealed that this translated PRO should be considered measuring a unidimensional trait, without using subscale scores [27,28].

MHQ. The Michigan Hand Outcome Questionnaire (MHQ) rates hand-specific outcomes and contains six subscales: general hand function, daily functioning, work, pain, esthetics and patient satisfaction with hand function. The scale score is the sum of the answer to each question and ranges from 0 to 100. A higher score in the pain scale indicates more pain. For the other five scales, higher scores imply a better hand performance [29]. The MHQ is a reliable and valid questionnaire for measuring hand outcome in patients with varying hand problems [29,30]. The MHQ has not yet been validated in the Dutch translated version.

SF-36. The Short Form Health Survey (SF-36) contains 36 questions about a patients' health status. Nine subscales are distinguished: physical functioning, social functioning, role limitation physical, role limitation social, mental health, vitality, pain, general health and health change. Each subscale ranges from 0 (maximum disability/pain) to 100 (no disability/pain) [31]. Jenkinson *et al*. have shown that the validity of this questionnaire is sufficient for groups reporting varying extents of illness-health [31]. In addition, it has been validated in the Dutch language [32].

Statistical analysis

Paired samples T tests were used to determine statistical differences between functional outcome of injured and uninjured wrist. Welch tests were used to determine statistical differences between functional outcome or PROs between the PLD/PLFDs group and the matched control group. Because of multitesting, a p-value $<.01$ was considered statistically significant.

RESULTS

Study Population

PLD/PLFD group. A total of 24 patients with PLD/PLFDs were retrieved from hospital records. Three patients were excluded based on insufficient control of the Dutch language or dementia. Two patients could not be reached due to outdated contact information. Eight patients refused to participate. Finally, a total of 11 patients were included (9 males) with median age at injury of 38 years (IQR 33; 54). Median follow up time was 97 months (IQR 84-193) (Table 1). Five patients had sustained a fracture of the scaphoid. The capitate was fractured in one patient and the ulnar styloid was fractured in two patients. Six patients had transient median nerve neuropraxia. All PLD/PLFDs were surgically treated within five days following the injury. Four patients underwent secondary surgery because of re-dislocation, three within nine days after initial surgery, one at two years after initial surgery. Approximately two years after the injury, one patient underwent a four-corner arthrodesis and another patient underwent a complete wrist arthrodesis. Seven patients received specific rehabilitation programs for the PLD/PLFD, while 4 did not (Table 1).

Matched control group. Twenty-two control patients were matched with the eleven included PLD/PLFD patients: no significant differences were found in age or gender between the groups (Table 1).

Clinician reported outcomes

Within patients with PLD/PLFD flexion/extension and ulnar/radial deviation were significantly worse in the injured compared to the uninjured wrist (mean difference -54°, 95% CI -77, -31, P<.001 and mean difference -29°, 95% CI -37, -20, p<.001), even when excluding patients with an arthrodesis (Table 2). For grip strength measurements in comparison to the uninjured wrist, only grip strength (mean difference -12.7 kg, 95% CI -19.7, -6, p=.002) was significantly worse in the injured wrist (Table 2). Patients without arthrodesis did not have a significant difference in grip strength between the injured and uninjured wrist. Grip strength of the patients' injured side was median 80% of the uninjured side. Four patients had grip strength < 75% of the uninjured side.

Flexion/extension (mean difference -60°, 95% CI -76, -43, p<.001) and ulnar/radial deviation (mean difference -28°, 95% CI -38, -18, p<.001) were significantly diminished in patients with PLD/PLFD in comparison to matched controls. When excluding patients with an arthrodesis, flexion/extension and ulnar/radial deviation remained significantly diminished in patients with PLD/PLFDs (Table 3). With regard to all grip strength measurements, no significant differences were present between patients with PLD/PLFDs and matched controls (Table 3).

Table 1. Patient characteristics of the PLD/PLFD group (N=11) and the matched control group (N=22)

	PLD/PLFD group	Control group
Male : Female	9 : 2	9 : 2
PLD : PLFD	4 : 7	-
Dominant side Left : Right	1 : 10	0 : 22
	Median (IQR)	**Median (IQR)**
Age at time of injury (years)	38.0 (33.0;54.0)	-
Age at follow-up (years)	48.0 (40.0;63.0)	48.5 (39.5;64.3)
Delay surgery (days)	0 (0;1)	-
Follow-up (months)	97 (84;193)	-
	N	**N**
Dominant side injured	4	-
Surgical approach		-
dorsal	2	
volar	5	
combined approach	1	
percutaneous	3	
Surgical procedure		-
K-wire	3	
screw	1	
K-wire and screw	3	
K-wire and fragment fixation system	1	
screw and external fixation	1	
K-wire, screw and external fixation	2	
Secondary surgery	4	-
arthrodesis	2	
Rehabilitation program	7	-

N= number of patients/participants, IQR: interquartile range 25^{th} - 75^{th} quartile, PLD= perilunate dislocation, PLFD= perilunate fracture dislocation, K-wire=kirschner wire

Table 2. Functional outcome between injured and uninjured wrist for PLD/PLFD patients. Results of Paired samples T test

All patients	**Injured wrist (N=11)** **Mean (SD)**	**Uninjured wrist (N=11)** **Mean (SD)**
Range of motion (°)		
Flexion/extension	90 (27)	144 (16)
Ulnar/radial deviation	33 (14)	61 (10)
Supination/pronation	155 (12)	162 (9)
Grip strength measurements (kg)		
Grip strength	35.3 (16.0)	48.0 (13.0)
Sustained grip strength	22.3 (11.9)	30.0 (10.2)
Key pinch strength	8.5 (1.7)	9.2 (2.4)
Patients without arthrodesis	**Injured wrist (N=9)** **Mean (SD)**	**Uninjured wrist (N=9)** **Mean (SD)**
Range of motion (°)		
Flexion/extension	97 (23)	142 (16)
Ulnar/radial deviation	35 (10)	62 (10)
Supination/pronation	157 (10)	163 (10)
Grip strength measurements (kg)		
Grip strength	33.9 (17.5)	45.6 (12.8)
Sustained grip strength	22.1 (13.3)	28.9 (9.7)
Key pinch strength	8.7 (1.8)	9.1 (2.4)

N= number of patients/participants, SD= standard deviation, 95% CI= 95% confidence interval of the difference, kg= kilogram

Mean difference (SD)	95% CI	*p*-value
-54 (34)	-77; -31	<.001
-29 (13)	-37; -20	<.001
-8 (9)	-14; -2	.016
-12.7 (10.4)	-19.7; -6.0	.002
-7.6 (9.8)	-14.2; -1.0	.027
-.7 (1.6)	-1.8; .3	.157

Mean difference (SD)	95% CI	*p*-value
-45 (29)	-67; -22	.002
-27 (12)	-36; -18	<.001
-6 (7)	-11; -1	.035
-11.7 (10.9)	-20.1; -3.3	.012
-6.7 (9.3)	-14.0; .4	.060
-.5 (1.5)	-1.6; .7	.365

Table 3. Functional outcome for PLD/PLFD patients and matched controls. Results of Welch test

All patients	**PLD/PLFD group (N=11)** **Mean (SD)**	**Control group (N=22)** **Mean (SD)**
Range of motion (°)		
Flexion/extension	90 (27)	150 (20)
Ulnar/radial deviation	33 (14)	61 (12)
Supination/pronation	154 (12)	164 (14)
Grip strength measurements (kg)		
Grip strength	35.3 (16.0)	45.1 (14.3)
Sustained grip strength	22.3 (11.9)	29.6 (10.6)
Key pinch strength	8.5 (1.7)	9.0 (2.4)
Patients without arthrodesis	**PLD/PLFD group (N=9)** **Mean (SD)**	**Control group (N=18)** **Mean (SD)**
Range of motion (°)		
Flexion/extension	97 (23)	149 (18)
Ulnar/radial deviation	35 (10)	60 (12)
Supination/pronation	157 (12)	163 (12)
Grip strength measurements (kg)		
Grip strength	33.9 (17.5)	44.3 (15.3)
Sustained grip strength	22.1 (13.3)	28.7 (11.3)
Key pinch strength	8.7 (1.8)	8.8 (2.5)

N= number of patients/participants, SD= standard deviation, SE= standard error, 95% CI= 95% confidence interval of the difference, kg= kilogram

Mean difference (SE)	95% CI	*p*-value
-60 (9)	-76; -43	<0.001
-28 (5)	-38; -18	<0.001
-10 (5)	-19; 0	0.055
-9.8 (5.7)	-22; 1	.103
-7.3 (4.2)	-16.2; 1.6	.102
-.6 (.7)	-2.1; 1.0	.455

Mean difference (SE)	95% CI	*P*-value
-52 (8)	-70; -33	<.001
-25 (4)	-34; -16	<.001
-7 (4)	-16; 1.9	.118
-10.4 (6.9)	-25.1; 4.3	.151
-6.6 (5.2)	-17.7; 4.5	.223
-.1 (.8)	-1.9; 1.6	.881

Table 4. Patient reported outcomes (PROs) for PLD/PLFD patients and matched controls. Results of Welch test

PROs	**PLD/PLFD group (N=11) Mean (SD)**	**Control group (N=22) Mean (SD)**
DASH	22 (20)	3 (6)
PRWE		
Pain	19 (14)	1 (2)
Function	19 (28)	0 (1)
Total	31 (22)	1 (3)
MHQ		
General function	59 (16)	94 (9)
Activities general life	84 (13)	99 (2)
Work	89 (20)	100 (0)
Pain	71 (26)	98 (4)
Esthetics	91 (11)	97 (11)
Satisfaction	63 (30)	99 (2)
Total	76 (15)	98 (3)
SF-36		
Physical functioning	86 (9)	93 (15)
Social functioning	80 (31)	95 (12)
Role model physical problem	61 (41)	88 (30)
Role model emotional problem	85 (35)	95 (21)
Mental health	75 (19)	89 (11)
Vitality	67 (21)	82 (15)
Pain	68 (22)	90 (14)
General health experience	67 (11)	78 (14)
Health change	45 (10)	51 (14)

N= number of patients/participants, SD= standard deviation, SE= standard error, 95% CI= 95% confidence interval of the difference

Mean difference (SE)	95% CI	*p*-value
19 (6)	6; 33	.010
19 (4)	9; 28	.001
19 (8)	0; 38	.047
30 (7)	15; 45	.001
-35 (5)	-46 ; -24	<.001
-16 (4)	-25 ; -7	.003
-11 (6)	-24 ; 2	.095
-28 (8)	-45 ; -10	.006
-6 (4)	-14 ; 3	.170
-36 (9)	-57 ; -16	.002
-22 (5)	-32 ; -12	.001
-6 (4)	-16; 4	.209
-15 (10)	-36; 6	.138
-26 (14)	-56; 3	.078
-11 (11)	-35; 14	.366
-14 (6)	-27; 0	.046
-15 (7)	-30; 0	.051
-22 (7)	-38; -7	.008
-11 (4)	-20; -1	.019
-7 (4)	-16; 3	.139

Patient reported outcomes

Pain. Pain was significantly higher in the PLD/PLFD group compared to the control group as measured on all pain subscales (Table 4).

Physical functioning. Hand function, daily functioning and general physical functioning were significantly worse in the PLD/PLFD group compared to the control group as measured with the total DASH score (mean difference 19, 95% CI 10, 28, p=.010), total PRWE score (mean difference 30, 95% CI 0, 38, p=.001, MHQ subscale general functioning scale (mean difference -35, 95% CI -46, -24, p=<.001), MHQ subscale activities general life (mean difference -16, 95% CI -25, -7, p=.003). The PRWE function score and the SF-36 physical functioning subscale was not significantly different between patients with PLD/PLFDs and matched controls (Table 4).

Satisfaction. Patients were less satisfied with their wrist compared to the controls (mean difference MHQ subscale satisfaction -36, 95% CI -57, -16, p=.002).

General health status. Although not significant, patients did seem to experience an impact on overall health status, as can be retrieved from the SF-36 subscale general health experience (mean difference -11, 95% CI -20, -1, p=.019) (table 4).

Work. Two of the nine working PLD/PLFD patients had to alter their occupation following injury because physical demands for the injured side were too high in the original occupation.

DISCUSSION

On average 8 years after they sustained the injury, PLD/PLFD patients experienced a decreased range of motion of the affected wrist and a substantial amount of pain. They were less satisfied and reported diminished daily and general physical functioning. The significant disability of PLD/PLFD patients, which has previously been described using mainly functional outcomes, was confirmed in the current research. Especially the application of a wide variety of PROs provided new insight in the impact of PLD/PLFDs on every day life regarding pain, physical functioning, satisfaction and health status patients experience following PLD/PLFDs.

Clinician reported outcomes

Range of motion. Diminished flexion, extension, ulnar and radial deviation of the wrist after PLD/PLFD was described previously [3,8,11,13,33]. We hypothesize that the decrease in range of motion may be caused by posttraumatic arthritis or ligamentous injury, even when adequate surgical treatment has been provided. However, our study cannot confirm this, because no radiographs were taken at follow-up. Pro- and supination of the wrist were not affected, probably because these movements are regulated mostly in the elbow and the distal radio-ulnar joint [34].

Grip strength. Grip strength measurements were comparable in patients and controls, although a significant difference was found within the PLD/PLFD patients between the injured and uninjured side of which 4 patients had grip strength measurements of < 75% of the uninjured wrist. An explanation could be overcompensation of the uninjured hand resulting in relatively high grip strength and sustained grip strength in that hand. These findings imply that the injured side needs extra attention to increase strength, for example by applying specific training programs. Compared to literature our results reflect a reasonably good outcome [9,23]. Capo *et al.* reported grip strength following PLD/PLFDs of only 59% in comparison to the unaffected side [8]. The substantial decrease in grip strength was probably caused by additional upper limb fractures in some of the PLD/PLFD patients in that study. Grip strength is regulated mainly by the strength of a chain of muscles like forearm muscles, biceps and triceps muscles, which are not affected in PLD/PLFD patients [35].

Patient reported outcomes

Pain. All pain scales showed that patients experienced more pain than the matched controls. Clinicians treating these patients should therefore realize that pain is a considerable problem in PLD/PLFD patients and treat these patients accordingly, e.g. by prescribing pain medication and proposing rehabilitation strategies. If all non-operative treatments fail, partial or complete wrist denervation might be a successful, although mostly temporary, solution [36-38]. Wrist denervation is a symptomatic treatment and selectively eliminates the anterior and posterior interosseous nerves, which innervate the central two-thirds of the anterior and posterior carpal joint capsule, respectively [39]. Removal of these sensory innervations of the wrist joint provides relief of pain, while maintaining function and mobility of the hand and wrist [39]. Studies report satisfactory results with short term follow up. One third of the patients need revision surgery at longer follow up duration [36,37]. In addition, several authors state that the degree of pain relief following wrist denervation is inadequate for patients who perform heavy manual labour [19,38]. Another surgical treatment option for patients following PLD/PLFDs with pain is (partial) arthrodesis [12,19]. Many techniques have been described, including arthroplasty, limited or total fusion, partial or total joint replacement, interpositional arthroplasty and rib cartilage graft implantation [19]. It is important to indicate with physical examination, radiographs and computed tomography, what joints are causing the painful wrist before choosing a technique [19]. Laulan *et al.* suggest an algorithm for choosing the right treatment on basis of the severity of the scapholunate advanced collapse (SLAC), volar/dorsal intercalated segment instability (VISI/DISI) of the proximal carpal row and patient characteristics [18]. However an arthrodesis may not help all: the patient in our study who received the four-corner arthrodesis remained to have moderate pain [40,41]. Martini *et al.* stated that the use of a partial arthrodesis is only a temporary solution for treating pain [42]. Following a total wrist arthrodesis a mean VAS of 2/10 combined with 80-90% of normal strength can be expected and most patients are able to return to their previous occupation [18]. In addition, patients rarely perceive the loss of mobility as problematic and patient satisfaction rates range from 80-100% [43].

While local surgical procedures might diminish pain sensation, there is growing evidence that chronic pain is also a determinant of changes in the central nervous system following surgical trauma or nerve injury [44]. The pathophysiological pathway is caused by nociceptive transmission and inflammatory mediators released during surgical procedures [44,45]. In addition, several risk factors for the development of postoperative chronic pain are determined, such as preoperative pain lasting longer than 1 month, psychological vulnerability, worker's compensation and younger age [45]. These risk factors might be applicable to patients with PLD/PLFDs. Reducing the risk of development of chronic pain can be achieved with good perioperative and postoperative pain management. This results in reduced central sensitization [44]. In addition, managing expectations of patients and careful explanation of surgical procedures and postoperative rehabilitation is known to reduce anxiety and promote recovery [46,47]. It is important, while treating these patients, to be aware of the risk factors for the development of chronic pain and to implement shared-decision making.

Physical functioning. The PLD/PLFD group experienced more problems in daily activities than the control group. The DASH outcomes reported in this study were similar to those described in previous studies in PLD/PLFD patients [9,11]. Capo *et al.* described worse DASH score, this could be explained by additional upper limb fractures the patients in their study had and the fact that they did not obtain a DASH score for all of their patients [8]. In our study the mean total

PRWE score was 31, which was worse than reported in the studies of Forli *et al.* and Strobel *et al.* [12,13]. The time to surgical treatment was comparable in our study, but the dominant hand was more frequently affected in those studies (44% and 90%) compared to our study (33%) [12,13]. It might be that recovery of an injured dominant hand has a better prognosis, because of its preferred and more intuitive use in daily practice.

Satisfaction. An interesting finding of our study was the poor satisfaction in the PLD/PLFD group. In a post hoc exploration of outcomes of the items of the MHQ satisfaction subscale showed that patients were particularly dissatisfied about range of motion, grip strength and pain. However, none of these patients sought help for these symptoms. Especially the dissatisfaction about grip strength needs attention in further research, since grip strength measurements did not reveal any differences with control persons. However, comparison of the patients' injured and uninjured side revealed significant lower grip strength in the affected limb, which apparently bothered the participants in their daily life. Until now, satisfaction has not gained attention in literature on PLD/PLFD. As patients nowadays are stimulated to manage their own treatment and be responsible for their recovery as much as possible, patient satisfaction seems to be a relevant topic for future research. Correct briefing of the patients about the eventual outcomes after rehabilitation, including satisfaction issues, may be relevant to improve outcomes in this population. Although the MHQ is mainly developed for patients with rheumatoid arthritis and has not been used in PLD/PLFD patients before, we have shown with the current study that this questionnaire includes relevant topics for these patients [29,30]. The reason for the good applicability of the MHQ is the multidimensionality of the questionnaire, measuring more than just the standard subscales of pain and function.

Overall health status. In addition to diminished injury-specific PROs (pain, physical functioning), patients also experienced diminished general health status in comparison to healthy controls. In literature, only Strobel *et al.* describe general health outcome measures following PLD/PLFDs using the total SF-36 score (mean 78, SD 23) in patients with mean age of 30 years and after a follow up duration of 67 months [12]. Unfortunately, the subscales of the SF-36 are not presented in this study, so no reliable comparison with the results in our study can be made. However, the diminished outcomes in both studies do present an impact of PLD/PLFDs on general health experience. This finding is worrisome and should gain more attention in clinical practice.

Work. Despite pain, lower hand function, less satisfaction and overall diminished experience of general health, the PLD/PLFD patients did not differ from their matched controls regarding work participation. There is no literature reporting validated questionnaires regarding occupation, work participation or work productivity. For further research, it would be interesting to investigate whether sick leave, quality of work and work productivity are also comparable between both groups.

Strengths and weaknesses

The use of a matched control group, two times the size of that of patients is a unique and valuable contribution to present research about PLD/PLFDs. The severity of limitations in pain and physical functioning as experienced by the PLD/PLFD patients can be interpreted in comparison with people of their age and gender. Furthermore, results of a substantial number of validated questionnaires were reported, which are rarely described in literature. The measurements of the CROs were performed by two researchers. This might have created a small measurement bias, even though the author performing the measurements received extensive training from the certified hand therapist. Finally, the biggest challenge of this descriptive cohort study was the scarcity of the injury, which resulted in a small number of PLD/PLFD patients. To achieve respectable research quality, a larger sample size is required by performing prospective multicenter research in the future.

Clinical implications

The study results enable informing PLD/PLFD patients about their expected recovery and outcome. A patient will now know that the flexion/extension and ulnar/radial deviation might remain limited. Informing patients about the expected outcome and providing a patient tailored rehabilitation program is mandatory. Specific attention should be paid to strength rehabilitation of the injured wrist, since we found a significant difference in grip strength between injured and uninjured wrists. Pain, restrictions in daily life function and diminished general health status are likely to be present and patients should be informed about this. It is advisable to use PROs in the rehabilitation program to investigate what implications the PLD/PLFD has on a patient's life and act accordingly. The restrictions patients experience following PLD/PLFDs seem however unlikely to force patients to change their occupation, although individual results show that some minor adjustments at work may be needed. Clinicians need to be alert that pain plays a major role in the life of a PLD/PLFD patient. It is important to recognize risk factors for the development of chronic pain, treat chronic pain when it is present with a combination of optimal pain relieve, shared-decision making and rehabilitation strategies. In addition, partial or complete wrist denervation might be a successful temporary option for patients who do not perform heavy manual labour. Other surgical treatment options include several types of partial or complete wrist arthrodesis. When choosing a type of wrist arthrodesis, it is important to exactly indicate what joints are causing the painful wrist.

Conclusions

A PLD/PLFD has a significant impact on everyday life, as patients experience diminished range of motion, pain, diminished physical functioning, diminished satisfaction and report lower general health status than healthy controls. However, no consequences for work participation were found in this study.

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PART 2

Validation of patient reported outcome measures

CHAPTER 6

Structural validity of the Dutch version of the Disability of Arm, Shoulder and Hand questionnaire (DASH-DLV) in adult patients with hand and wrist injuries

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ABSTRACT

Introduction. Fractures of the hand and wrist are one of the most common injuries seen in adults. The Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire has been developed as a patient-reported assessment of pain and disability to evaluate the outcome after hand and wrist injuries. Patient reported outcomes (PROs) can be interpreted as pain, function or patient satisfaction. To be able to interpret clinical relevance of a PRO, the structural validity and internal consistency is tested. The Dutch version of the DASH has not yet been validated.

The aim of this study was to evaluate the structural validity and the internal consistency of the existing Dutch version of the DASH. The relevance of reporting subscale scores was investigated.

Methods. This study was a retrospective analysis of cross-sectional data of 370 patients with an isolated hand or wrist injury. Adult patients aged 18 to 65 years treated conservatively or surgically were included. Patients unable to understand or read the Dutch language were excluded. Confirmatory factor analysis was used to investigate the structural validity, while Cronbach's alpha and coefficient omega were used to assess internal consistency.

Results. All investigated models (a single factor model, a 3-correlated factor, and a bifactor model) were associated with a good model fit. Both the single factor and the 3-correlated factor model were associated with factor loadings of at least 0.70. In addition, the covariance between the factors in the 3-correlated factor model was positive (at least 0.89) and statistically significant ($p<0.001$). In the bifactor model, the additional value of subscales was limited as the items loaded high on the general factor but low on the subscale factors.

Conclusions. This study indicates that the Dutch version of the DASH should be considered as an unidimensional trait. A single score should be reported.

INTRODUCTION

Hand and wrist injuries are commonly seen in adults [1–4]. About 20% of all visits to the emergency departments are due to hand and wrist injuries [5,6]. Considering the ageing of the population, the incidence for these injuries is going to grow [7,8].

The prevalence of chronic pain following distal radius fractures is reported to be as high as 30%. Of these patients, 11% report moderate to very severe pain one year after the initial injury [9,10]. Longterm disability largely affects elderly patients, of whom 46-95% report some degree of disability one year following the initial accident, and 7-16% even report moderate to very severe disability [9,10]. Aforementioned complaints may result in patients' inability to perform daily activities.

The International Classification of Functioning, Disability and Health, the ICF, provides a standard language and framework for the description of functioning and disability [11]. In the ICF, functioning problems are classified in three areas: Impairments, Activity limitations and Participation restrictions. The broad concept of disability can refer to any or all areas of functioning in the ICF. Patient reported outcomes (PROs) are one of the most common techniques to assess the different facets of functioning. These outcomes are reported by patients and not defined by an observer [12]. They may be used in clinical decisionmaking, as well as in health care policies and reimbursement decisions [13,14]. To ensure a PRO can be used in clinical practice for these abovementioned functions, they have to be validated [14]. Recently, recommendations for a core set of domains for standardized reporting in distal radius fracturs have been published [15]. Pain and function were considered as primary domains.

In every day practice, mostly traditional outcome measures are used to determine results of treatment. For hand and wrist injuries these include physical examining, range of motion, grip strength and radiographic imaging. These examinations mainly reflect aspects of disability in bodily functions. However, the traditional outcome measures are "clinician based" (clinician reported outcomes; CROs) and do not correlate well with aspects that patients find important, such as activity limitations [16]. Therefore, PROs are increasingly used to evaluate the result of treatment and rehabilitation, also in patients with hand and wrist injuries.

The American Academy of Orthopedic Surgeons, the Council of Musculoskeletal Specialty Societies and the Institute for Work and Health developed a questionnaire which reflects the impact of injury on function of a variety of upper extremity musculoskeletal disorders or injuries and developed the Disabilities of the Arm, Shoulder and Hand, questionnaire (DASH) [17]. The

DASH is a 30-item, self-report questionnaire to measure physical function and symptoms in people with musculoskeletal disorders of the upper limb [17]. The questionnaire consists of 3 subscales: a physical subscale, a symptoms subscale and the psychosocial subscale. The DASH has been translated and adapted into several languages [18,19,28–32,20–27].

In literature exploratory factor analyses (EFA) have been conducted by several authors in different languages to examine the underlying factors of the DASH questionnaire [22,33,34]. EFA is a data-driven method without making specifications about the number of and relationships between the latent factors. This approach is used as an exploratory technique. In contrast, confirmatory factor analysis (CFA) requires strong empirical or conceptual grounds to guide the specification and evaluation of the structure of the model in advance [35]. To date, only two studies reported on CFA of the DASH, which were performed on the Italian and American version of the DASH [36,37].

In this study, the structural validity of the existing translated Dutch version of the DASH (DASH-DLV) was investigated in a patient population with hand and wrist injuries [38]. Particularly, a CFA was conducted, followed by an assessment of internal consistency. Because Veehof *et al*. already translated the DASH into a Dutch version, we chose not to translate the DASH again [34].

METHODS

Patients

As described previously, adult patients who sustained an isolated hand or wrist injury in 2012 and 2013 were requested to participate in this cross-sectional study [39]. All patients were treated at a level I traumacenter in the Netherlands, either conservatively or surgically. Included patients had to be 18-65 years of age at the time of injury. Exclusion criteria were unability to speak or read Dutch. All of these patients were invited and sent a paper version of the DASH-DLV, and a reminder after 2 weeks, if needed. The local institutional review board (the Medical Ethics Committee of the University Medical Center Groningen) has reviewed the study protocol and waived further need for approval. In addition, the study was performed in compliance with the principles outlined in the Declaration of Helsinki on ethical principles for medical research involving human subjects [40].

Disability of Arm, Shoulder and Hand Questionnaire

In 1993, the need for a PRO that reflected the impact of a variety of musculoskeletal diseases and injuries of the upper limb on function was independently identified by researchers from the American Academy of Orthopaedic Surgeons' Outcomes Studies Committee and the Institute for Work & Health [41]. The goal was to develop a self-administered tool that would assess symptoms and physical function at the level of disability, with a focus on physical function, of any or multiple joints or conditions of the upper limb [42]. Item generation and item reduction based on clinimetric and psychometric principles resulted in a 30-item questionnaire [43,44]. The final 30-item DASH questionnaire includes 21 physical function items, six symptom items and three social/role function items, plus the optional four-item work and sports/performing arts modules.

Structural validity and internal consistency

Structural validity, defined as the degree to which scores of an instrument are an adequate reflection of the dimensionality of the construct to be measured, of the DASH-DLV was assessed by CFA [45]. A single factor model of the DASH-DLV (Figure 1), and a correlated 3-factor model ('physical function', 'symptom' and 'psychosocial' subscale, Figure 2) were explored. In addition, a bifactor model was investigated (Figure 3). A bifactor model includes a general factor associated with all test items and one or more group factors associated with a limited number of items [46]. The general factor and group factors are assumed to be uncorrelated. Bifactor models may be used when subscores are expected. Bifactor models are valuable in determining the contribution of subscale scores over and above the general factor [47]. All the investigated DASH-DLV models are presented in Figure 1, 2 and 3.

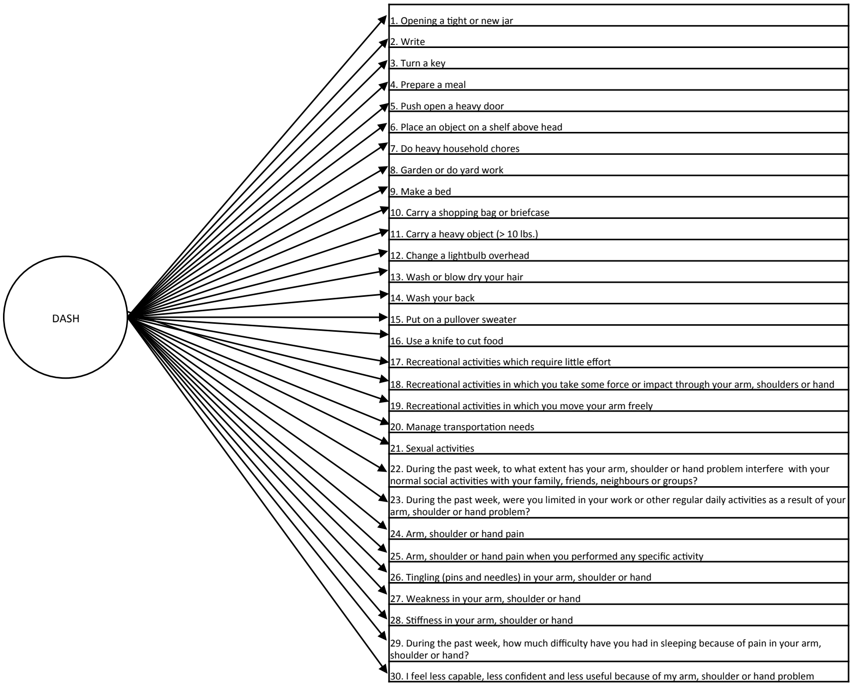

Figure 1. Model 1: a single factor model

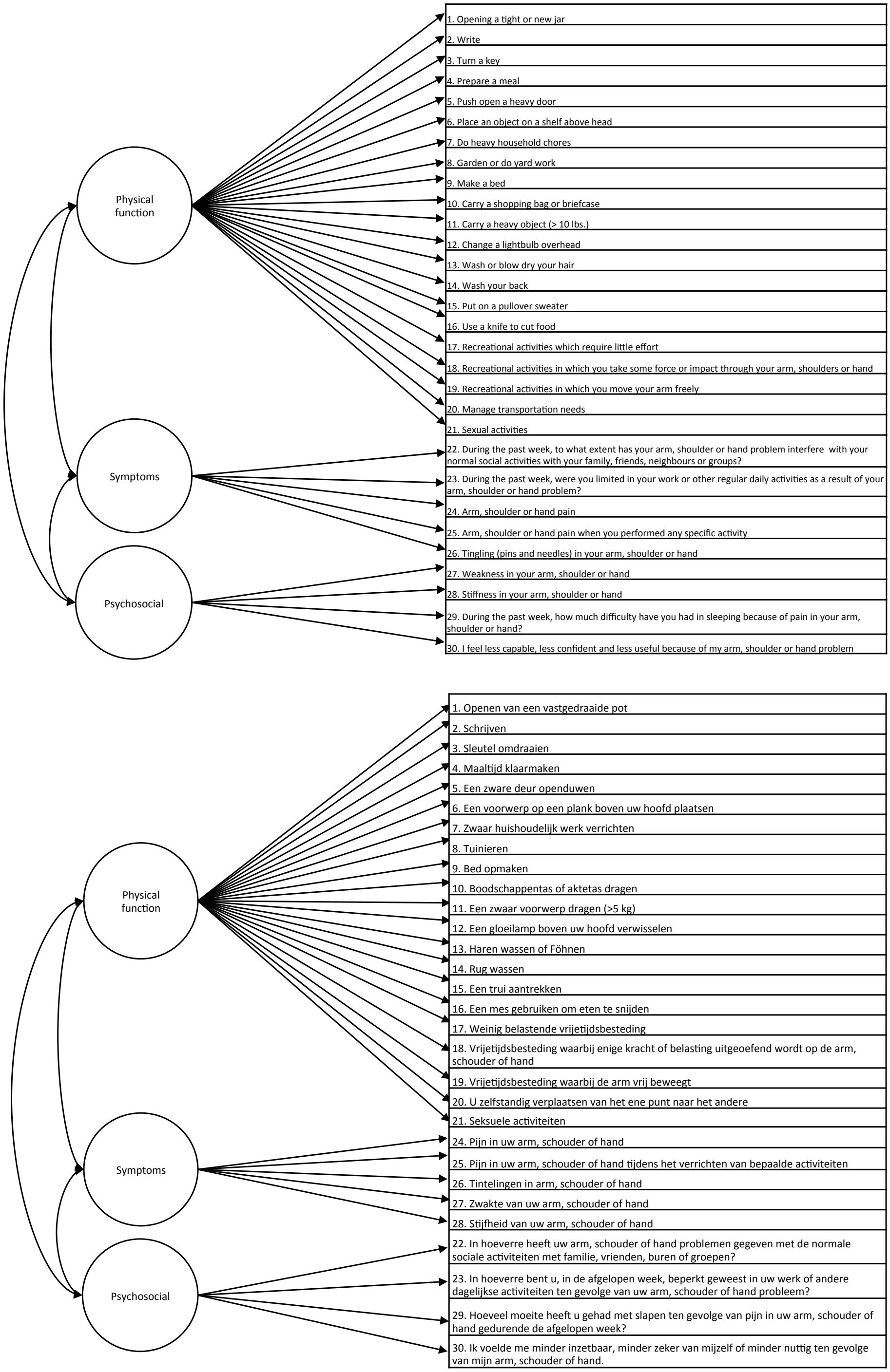

Figure 2. Model 2: a correlated 3-factor model

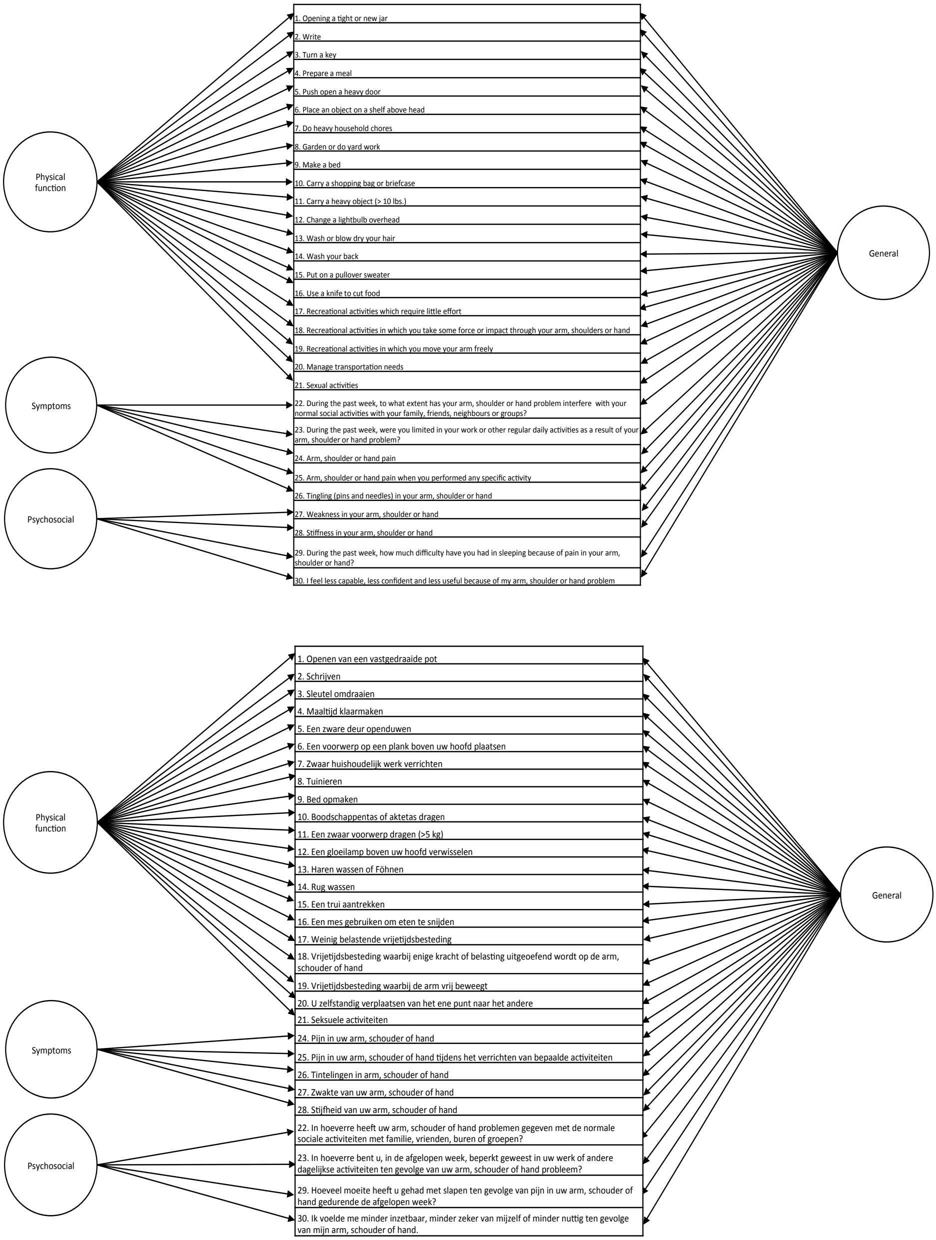

Figure 3. Model 3: a bifactor model

Internal consistency examines to what degree the items in a questionnaire are interrelated, and measure the same construct [48]. In this study, the internal consistency was determined after conducting a factor analysis to verify the dimensionality. Two approaches were used. First, Crohnbach's α was calculated for each (sub)scale. It represents a ratio between the true score variance and the total variance [48]. However, Crohnbach's α tends to overestimate the reliability of the general factor in a multidimensional data structure and can therefore be misleading in bifactor models [49–51]. Preferably, the coefficient omega total (ω_T), and omega hierarchical (ω_H) are used to estimate the internal consistency in a bifactor model [49,52].

Omega total (ω_T) is an estimation of the reliability of a factor combining the general factor and the group factor variance. Omega hierarchical (ω_H) coefficient gives the proportion of variance in scale scores accounted for by a general factor [52]. The coefficient ω_H can be extended to estimate the reliability of the group factors, controlling for that part of the reliability due to the general factor in a bifactor model, termed omega subscale (ω_S) [50,51]. These coefficients provide useful information to judge whether scores for a group factor can be interpreted with confidence or only the total score (general factor) should be reported. A Cronbach's α, coefficient omega total, omega hierarchical, or omega subscale of 0.70 – 0.95 were considered an appropriate reliability.

To evaluate whether our data is 'unidimensional enough', two 'factor strength' indices were calculated [51]. First, we used coefficient omega hierarchical [52]. A high ω_H value indicates that a composite score is reflected by a single common source, i.e. one common factor underlies item responses. In addition, we calculated the Explained Common Variance (ECV), which is the ratio of the variance explained by the general factor, divided by the variance explained by the general factor and the group factors. There are no criteria for ECV to determine whether the data is unidimensional enough, but a higher ECV is seen as a stronger indication for unidimensionality [53].

Statistical analyses

For validating a questionnaire, there are numerous ways to determine the sample size [54]. In this study, a sample size of 300 cases was chosen, as Comrey and Lee recommend for conducting a factor analysis [55]. Confirmatory factor analyses were conducted using the R's package *lavaan* [56,57].

The robust weighed least squares means and variance (WLSMV) estimator with mean- and variance-adjustment was used to fit the models. Completely standardized results were used to report the factor loadings and covariances.

For each model, the χ^2 goodness-of-fit statistic was computed as the test of global fit. However, this statistic calculation is sensitive to the sample size. Four other commonly used fit indices were calculated as well to evaluate model fit. These indices included the comparative fit index (CFI), the Tucker-Lewis Index (TLI), the root mean square error of approximation (RMSEA), and the standardized root mean square residual (SRMR). A CFI and TLI close to 0.95 or higher, a RMSEA close to or less than 0.06, and a SRMR close to or less than 0.08 were considered as adequate model fit [58].

RESULTS

As described previously, a cohort of 466 patients who sustained isolated hand or wrist injury were eligible, of which 370 (79.4%) patients (188 males and 182 females) participated in the current study, with a mean age of 43.6 (SD=14.2) years [39]. The majority of the hand and wrist injuries (82%) were treated conservatively. A large proportion of the injuries were fractures, mainly of distal radius (130/334) (Table 1). The follow-up time ranged from 1 to 25 months. The DASH-DLV questionnaire was completely filled in by 329 of the responders (88.9%). Sixteen patients (4.3%) had a missing response on the item "sexual activities". The rest of the items were missing in less than 3%. Total scores could be calculated according to the DASH manual for all patients [41].

Table 1. Frequencies of hand and wrist injuries

Injury	**Frequency (%)**
Distal radius fractures	132 (35.7)
Carpal fractures	44 (11.9)
Metacarpal fractures	61 (16.5)
Phalangeal fractures	99 (26.8)
Finger joint dislocations	31 (8.4)
Others	3 (0.8)
Total	**370**

The 3 CFA models with corresponding fit statistics are presented in Table 2, the standardized factor loadings are presented in Table 3. Although associated with a significant χ^2 goodness-of-fit (584.83, df=405, p<0.001) adequate levels of absolute (RMSEA and SRMR) and incremental fit indexes (CFI and TLI) were calculated for Model 1. All factor loadings for this model were higher than 0.70 (Table 3).

Model 2 also yielded a significant χ^2 goodness-of-fit value (498.12, df=402, p=0.001), but satisfactory absolute and incremental fit indexes. In Model 2, all items loaded high on one of the three correlated subscale factors *Physical*, *Symptoms* and *Psychosocial*. The factor loadings ranged from 0.75 to 0.95. Only 5 and 4 items loaded on subscale factors *Symptoms* and *Psychosocial*, respectively. The covariance between the correlated factors was positive and statistically significant (*Physical* versus *Symptoms* = 0.89, *Physical* versus *Psychosocial* = 0.94, *Symptoms* versus *Psychosocial* = 0.92, all *p*-values<0.001).

Table 2. Fit statistics for the 3 CFA models

	Chi-squared goodness of fit	**df**	***p*-value**	**RMSEA (90% confidence interval)**	**SRMR**	**CFI**	**TLI**
Model 1	584.83	405	0.000	0.035 (0.028 – 0.041)	0.055	0.993	0.992
Model 2	498.12	402	0.001	0.026 (0.017 – 0.033)	0.050	0.996	0.996
Model 3	419.96	375	0.054	0.018 (0.000 – 0.027)	0.041	0.998	0.998

df = degrees of freedom, p = p value, RMSEA = root mean square error of approximation,
CFI = comparative fit index, TLI = Tucker-Lewis index, SRMR = standardized root mean square residual

The bifactor Model 3 was associated with good levels of model fit indexes: χ^2 value of 419.96 (df=375, p=0.054), RMSEA=0.018, SRMR=0.041, CFI=0.998, TLI=0.998.

However, in Model 3, many items loaded high (ranging from 0.69 to 0.93) on the general factor, but low on the subscale factors (Table 3). As an example, the correlated model (Model 2) suggests that item 8 'Garden or do yard work' was a strong indicator of the 'physical' subscale (i.e. a factor loading of 0.93). In contrast, Model 3 (the bifactor model) indicated that item 8 was a weak indicator (i.e. a factor loading of 0.06).

The ECV is 0.92 in Model 3. The factor strength indexes are also presented in Table 3. The coefficient ω_H was high for the general factor (0.96), but ω_S was low for the group factors ('physical', 'symptoms' and 'psychosocial'; which were 0.01, 0.26 and 0.11 respectively). These results indicate that a large portion of the total variance is explained by the general factor, and only a very small portion of the total variance is explained by subscale factors. Regarding internal consistency, Crohnbach's α of the single and the 3-correlated factor models (Model 1 and 2) were high, ranging from 0.88 to 0.97. For the general DASH-DLV scores, the coefficient ω_H was estimated to be 0.96. For the subscale factors, however, the ω_S values were remarkebly low (<0.26 for each subscale factor). These findings suggest that the DASH-DLV measures a single factor model and that it is not beneficial to report subscale scores.

Table 3. Factorloadings of the 3 different confirmatory factor models

Correlated factor model					**Bifactor model**			
Model 1		***Model 2***			***Model 3***			
1-factor		3-factor			Bifactor (3-factor)			
Item	λ_1 ***DASH***	λ_1 ***Physical***	λ_2 ***Symptoms***	λ_3 ***Psychosocial***	λ_G	λ_{g1}	λ_{g2}	λ_{g3}
1	0.84	0.85			0.84	0.13*		
2	0.78	0.79			0.79	-0.13*		
3	0.82	0.83			0.83	-0.04*		
4	0.88	0.89			0.88	-0.17*		
5	0.85	0.85			0.85	0.24*		
6	0.90	0.90			0.90	-0.05*		
7	0.91	0.92			0.91	0.12		
8	0.92	0.93			0.93	0.06*		
9	0.90	0.90			0.90	-0.07*		
10	0.93	0.94			0.89	0.36		
11	0.91	0.92			0.88	0.40		
12	0.88	0.88			0.88	-0.10*		
13	0.85	0.85			0.83	-0.34*		
14	0.85	0.85			0.85	-0.18*		
15	0.89	0.90			0.88	-0.38*		
16	0.85	0.85			0.86	-0.17*		
17	0.88	0.90			0.89	-0.16*		
18	0.89	0.90			0.90	0.03*		
19	0.91	0.92			0.92	0.07*		
20	0.88	0.89			0.87	-0.25*		
21	0.80	0.81			0.80	-0.12*		
22	0.86			0.89	0.86			0.08*
23	0.90			0.94	0.89			0.37*
24	0.90		0.93		0.83		0.57	
25	0.91		0.95		0.86		0.37	
26	0.71		0.75		0.69		0.25	
27	0.89		0.95		0.88		0.22	
28	0.80		0.84		0.78		0.30	
29	0.86			0.89	0.86			0.09*
30	0.91			0.94	0.90			0.36*
($\Sigma\lambda^2$)	25.10	16.28	3.94	3.35	22.31	0.88	0.66	0.28
ECV					0.92			

Table 3. Continued

Correlated factor model					**Bifactor model**			
Model 1		***Model 2***			***Model 3***			
1-factor		3-factor			Bifactor (3-factor)			
Item	λ_1 ***DASH***	λ_1 ***Physical***	λ_2 ***Symptoms***	λ_3 ***Psychosocial***	λ_G	λ_{g1}	λ_{g2}	λ_{g3}
α	0.97	0.96	0.91	0.88				
ω_T					0.98†	0.97†	0.91†	0.90†
ω_H					0.96†			
ω_s						0.01†	0.26†	0.11†

Factor loadings are completely standardized estimates. All factor loadings were statistically significant except those marked with *. G = general factor, g = group factor, λ = factor loading, ECV = explained common variance, α = Cronbach's alpha, ω_T = omega total, and ω_H = omega hierarchical, ω_S = omega subscale † p<0.001.

DISCUSSION

The various CFA models were used to clarify how the items of the DASH-DLV relate to each other, and to explore if there were any subscale scores that should be used when scoring the questionnaire. This study suggests that the DASH-DLV reflects a unidimensional trait, and thus reporting subscale scores in the Dutch translation of the DASH is of very limited value and should be avoided.

The Upper Extremity Collaboration Group used principle component analysis to determine the dimensionality of the DASH. Although a two-factor model explained more variance and the scree plot suggested two factors, a one-factor model is recommended given its simplicity [41].

While principal component analysis aims to explain all variance in the data set, making it most appropriately applied as a data reduction technique, EFA is used to only explain the common variance of all items, discovering a set of yet unknown latent variables based on the data. In contrast, confirmatory factor analysis makes it possible to test whether the data fit a prehypothesized factor structure based on empirical data or theory, making this technique more appropriate to confirm the factor structure (i.e. dimensionality) of a questionnaire. The choice for a particular method of factor analysis is crucial, because the different techniques have different assumptions about the data and answer different research questions [59].

In this study, we used CFA since our reseach question was to confirm the factor structure of the DASH-DLV. To our knowledge, only two studies have conducted CFA to examine the DASH questionnaire [36,37]. Franchignoni *et al.* investigated the factor structure of the Italian version of the DASH [36]. After an exploratory approach, the 3-factor structure showed adequate fit, nonetheless with some misfitting items. A 1-factor model of the DASH was not confirmed as indicated by poor fit statistics.

In the American version, Lehman *et al.* also tested a 3-factor model after excluding item 20 and 21 because of their unacceptably low factor loadings [37]. Although the TLI and SRMR values indicated good fit, the CFI and RMSEA do not. In addition, they found high interfactor correlations (>0.83).

All models in our study yielded adequate fit to the data (Table 2). Both Model 1 (one-factor) and Model 2 (3-correlated factors) showed high and statistically significant factor loadings. However, the subscales 'symptoms' and 'psychosocial' of Model 2 included only 3 and 2 items, respectively, potentially compromising the coverage of the construct's theoretical domain. All items in the bifactor model (Model 3) were associated with high factor loadings on the general factor, but low on the group factors. Bifactor analysis allows researchers to empirically examine the appropriateness of using subscales. To date, research in assessing the structural validity of DASH has not included bifactor models.

Several important findings support that the DASH-DLV is sufficiently unidimensional. First, the covariance between the 3 correlated factors in Model 2 were all positive and significant, indicating unidimensionality. Second, the factor loadings of the general factor in the bifactor model (Model 3) are very similar to the loadings in the single factor model (Model 1). Furthermore, the factor loadings are high and statistically significant on the general factor, but substantially lower on the group factors. This suggests that the subscale factor contribution 'over and above' the general factor is very limited [47]. Third, the general factor of Model 3 accounted for more than 90% (ECV=0.92) of the common variance, indicating a high degree of unidimensionally. Finally, although the coefficient omega total values estimated in the bifactor model showed very good reliability for the general and subscale factors, the values of omega hierarchical of the general factor differed significantly from the omega subscale of the subscale factors. Omega hierarchical (ω_H) coefficient gives the proportion of variance in scale scores accounted for by a general factor, whereas the omega subscale represents the reliability estimate of the subscales, accounting for the effects of the reliability due to the general factor in bifactor models [52,60]. The coefficient omega hierarchical therefore provides useful information on whether scores for subscale factors can be interpreted with confidence, or that only the general factor score should be used. In this study, ω_S was very low for the subscale factors (ranging 0.01 – 0.26), but ω_H was high (0.96) for the general factor. This indicates that the subscale factors account for only 1 to 26%, while the general factor accounts for 96% of the variance. This implies that reporting subscale scores in the DASH-DLV is of extremely limited value.

This study has some limitations. The patients who were included mainly experienced distal radius fractures, and were mostly treated non-surgically. This distribution of patients may limit the generalizability of the results. For this study, we only included trauma cases and no elective cases. This may have caused a selection bias towards elderly females. In addition, an existing Dutch translation of the DASH questionnaire was used without employing a translation and culturally adaptation process. However, this Dutch version is widely used and supported by the Institute for Work & Health [38]. Despite these limitations, the response rate was sufficiently high and an adequate sample size was included. There was only a small number of missing values, from which total scores for all patients could still be calculated according to the DASH manual [41]. Finally, future studies should assess validity in more detail, and other measurement properties of the DASH, such as test-retest reliability and responsiveness, should be evaluated.

Conclusions

In conclusion, this study suggests that the DASH-DLV reflects a unidimensional trait, and thus reporting subscale scores in the Dutch translation of the DASH is of very limited value and should be avoided. Further studies should assess the validity of the DASH-DLV in more detail, as well as other measurement properties, such as test-retest, reliability, measurement error and responsiveness, to ensure reliable interpretation of this patient reported outcome measure in clinical practice.

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CHAPTER 7

Structural validity and construct validity of the Dutch-Flemish PROMIS® Physical Function - Upper Extremity version 2.0 item bank in Dutch patients with upper extremity injuries

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ABSTRACT

Introduction. Aim of this study was to validate the Dutch-Flemish Patient-Reported Outcomes Measurement Information System Physical Function - Upper Extremity version 2.0 item bank in patients with upper extremity injuries.

Methods. Cross-sectional study. Structural validity was assessed using Confirmatory Factor Analysis examining unidimensionality. In addition, a bi-factor model was fitted. Internal consistency was assessed by Cronbach's alpha. Construct validity was examined by assessing correlations with legacy instruments Disabilty of Arm Shoulder and Hand, Patient Reported Wrist Evaluation and Michigan Hand Questionnaire subscale Activities in Daily Life.

Results. A total of 303 patients (144 female) with mean age of 50 years (standard deviation 18) were included. Confirmatory Factor Analysis showed Comparative Fit Index of 0.94, a Tucker Lewis Index of 0.93, a Root Mean Square Error of Approximation of 0.12 and a Standardized Root Mean Residual of 0.09. Factor loadings were all above 0.70. Bifactor analysis showed an omega-H of 0.79 and Explained Common Variance of 0.67. The correlations with the legacy instruments were as expected or higher than expected.

Conclusions. The Dutch-Flemish Patient-Reported Outcomes Measurement Information System Physical Function - Upper Extremity version 2.0 item bank measures a unidimensional trait and sufficient construct validity was found.

INTRODUCTION

Every year many people suffer from musculoskeletal injuries. A recent study performed in the Netherlands showed a prevalence varying from 20-56% [1]. Especially upper extremity injuries form a major problem for society. They have a lot of impact on physical health, but also on work, daily activities, participation, and health care costs. Huisstede *et al.* showed that the prevalence of upper extremity injuries vary between 1.6-53% [2]. Although exact prevalence numbers are lacking, probably due to different ways of defining injuries of the upper extremity and the differences in rehabilitation strategies [2].

In daily clinical practice, patients' rehabilitation outcome after suffered upper extremity injuries is objectified using clinical measurements, e.g. grip strength, range of motion and radiological parameters. Other aspects such as pain, activity limitations, and participation restrictions are not being taken into account by these traditional methods [3]. Nowadays patient reported outcomes (PROs) are used more frequently, to consider both patient- and expert opinion-based outcomes. Using PROs improve communication between patient and expert, which improves treatment and rehabilitation strategies [4, 5].

Most frequently used PROs for upper extremity injuries include the Disability of the Arm, Shoulder and Hand (DASH) [6] questionnaire, the Patient-Rated Wrist Evaluation (PRWE) questionnaire [7], and the Michigan Hand Outcomes Questionnaire (MHQ) [8]. In general, there is some variation in the psychometric properties, and the concepts measured are not always well defined [9-12]. In addition, completing PROs is time-consuming for patients, and interpretability of the outcomes is sometimes unclear [9-12].

Because of these challenges, the Patient-Reported Outcomes Measurement Information System (PROMIS) was initiated by six US research centres and the National Institutes of Health. PROMIS contains a series of item banks with items focussed on function or pain, to measure outcomes from the patients' perspective across medical conditions [13]. The goal was to improve measurement quality and comparability of PROs and reduce patients' burden. Item banks were developed and validated for measuring specific symptoms and health status domains [13, 14].

The PROMIS Psychical Function item bank has been developed, validated and calibrated in the English language [15, 16]. To use the PROMIS item bank in the Netherlands and Belgium, the item bank was translated into the Dutch-Flemish language by the Dutch-Flemish PROMIS Group [17]. The first version of the Dutch-Flemish PROMIS Physical Function item bank (v1.2) contained 121 items [15-17]. This item bank has been validated in Dutch patients with chronic pain, patients undergoing physiotherapy, and patients with rheumatoid arthritis [18-20]. The PROMIS Group continued to improve the item bank, and a separate item bank for upper extremity injuries was developed, containing 46 items; the PROMIS® Physical Function - Upper Extremity (UE) v2.0 item bank (DF-PROMIS-UE v2.0) [21, 22]. Eventually, the item bank will be used as a Computerized Adaptive Test (CAT). The CAT system uses an algorithm that selects questions from the item bank based on the patients' response to the previous questions. When a predefined precision is reached, the system automatically stops asking questions. The benefit of a CAT is that the number of questions that need to be asked can be reduced to between 4 and 7 items [23].

The aim of this study was to validate the DF-PROMIS-UE v2.0 item bank. Structural validity and internal consistency must be sufficient before the item bank can be used as CAT. This ensures incorporating the patients' perspective on outcome following upper extremity injury and rehabilitation.

METHODS

For this cross-sectional study, patients with upper extremity injuries were recruited at the outpatient clinic of a level 1 traumacenter in the Netherlands from May until July 2018. All patients were treated, conservatively or surgically. Online written informed consent was obtained.

Inclusion criteria were: patients having an injury of the upper extremity, age of 18 years or older at the moment of completing the questionnaire and sufficient understanding of the Dutch language in reading and writing. *Exclusion criteria* were: no sufficient knowledge of the Dutch language. Uncompleted questionnaires were not included in the analysis.

Dispensation for medical ethical approval was granted by the local Medical Ethics Committee [2018.259]. In addition, the study was performed in compliance with the principles outlined in the Declaration of Helsinki on ethical principles for medical research involving human subjects [24].

Methods of measurement

The international *PROMIS guidelines* for instrument development and validation were used, which serves as the scientific foundation for questionnaire development and validation [25]. The guideline follows the following structure: First, translation has to take place. Second, cognitive debriefing needs to be performed to ensure understanding and readability of the translated questions. Third, validation should be performed [25].

Patients were requested to complete an online questionnaire, containing 4 questionnaires (108 items in total): the DF-PROMIS-UE v2.0 item bank (containing 46 items), the DASH (containing 30 items), the PRWE (containing 15 items) and the MHQ subscale Activities in Daily Life (MHQ-ADL, containing 17 items). The complete questionnaire was built in 'Survalyzer®', which is an online survey software program.

Following informed consent, the included patients completed the questionnaires on an electronic device (e.g. iPad, smartphone, computer), during their visit to the outpatient clinic or at home through an email with the link to the web-based questionnaire. Patients who were unable to use an electronic device could complete a paper version of the questionnaire. If applicable, a reminder by email was sent following the initial invitation. The estimated time to complete the online questionnaire was calculated to be about 13 minutes, based on an average expected response time per item of 7 seconds (108 x 7s) [26].

Measurements

The online questionnaire also contained questions addressing demographic and clinical characteristics. Demographic characteristics asked were age, gender, country of birth, expected duration of rehabilitation, and educational level. In addition, if present a pending compensation claim was recorded. Clinical characteristics that were asked were dominance, trauma intensity (mono-trauma or poly-trauma), disease duration at the moment of inclusion and the presence of other pain complaints.

The questionnaire of specific interest was the DF-PROMIS-UE v2.0 item bank. The first version (v1.2) of the Physical Function item bank measures general physical function, of both upper and lower extremity and health condition together [16]. A specific item bank focussing on upper extremity limitations was developed. Forty-two relevant items of the v1.2 item bank were reused, and 4 new upper extremity functioning questions were developed and translated into Dutch-Flemish. Following translation, to evaluate the comprehensibility and relevance of the items, cognitive debriefing was performed. Cognitive interviews were conducted for all 45 items with at least 5 native Dutch and at least 5 native Flemish patients and people from the general population (submitted for publication).

The current version of the PROMIS UE v2.0 item bank contains 46 items focussing on limitations in activities that require the upper extremity, with two different 5-point Likert response scales (Table 1). Scores of all PROMIS measures are expressed as T-scores, where a score of 50 represents the average of the (US) general population, with a standard deviation (SD) of 10. Higher scores indicate better function.

Table 1. DF-PROMIS-UE v2.0 item bank

DF-PROMIS-UE v2.0	46 items • 42 items specifically addressed to UE function. • 4 recently added items addressing UE function. Timeframe: none, but current status is inferred. Two different 5-point Likert response scales: • Unable to do/With much difficulty/With some difficulty/With a little difficulty/Without any difficulty • Cannot do/Quite a lot/Somewhat/Very little/Not at all Higher scores indicate better function: 0 (not able to do anything) to 100 (no disability at all)

As mentioned earlier, 3 disease specific legacy instruments were used in this study (DASH, PRWE and MHQ-ADL; Table 2.

The DASH questionnaire contains 30 items, specifically addressed to disabilities and symptoms in injuries of the upper extremity (Table 2) [6]. The questions use 5-point Likert response scales, ranging from no problems with functioning at all (1 point) until completely unable to function (5 points). The total score ranges from 0 (no disability) to 100 (most severe disability). The timeframe for the items is 'during the past week'. Both the primary English DASH questionnaire and the official Dutch translation have acceptable psychometric properties [11, 12, 27-31].

The Patient Rated Wrist Evaluation (PRWE) questionnaire contains 15 items, focused on wrist injury (Table 2) [7]. Five items are specifically addressed to pain and 10 items to function, divided into specific activities and usual activities. The timeframe for the items is 'during the past week'. The items assessing pain are rated from no pain (0) to unbearable pain (10), and the function scale is rated from no disability (0) to most disability (10). Higher scores imply worse outcome. Both the primary English PRWE questionnaire and the Dutch translation have acceptable psychometric properties [3, 7, 32].

The Michigan Hand Outcomes Questionnaire subscale Activities in Daily Life (MHQ-ADL). The complete MHQ contains 57 items [8], divided into 6 subscales; activities of daily living (ADL), overall hand function, pain, work performance, aesthetics and patient satisfaction with their hand function. For this study, the subscale MHQ-ADL was chosen, because the ADL subscale is expected to measure the same construct as the Dutch-Flemish PROMIS UE v2.0 item bank (Table 2). The MHQ-ADL contains 17 items, focused on hand or wrist injury [8]. Five items for the right hand, 5 items for the left hand and 7 items for both hands, all addressed to activities of daily living. Scores of the injured side were used for calculations. A 5-point Likert response scale is used: Not difficult at all/A little difficult/Somewhat difficult/Moderately difficult/Very difficult. The timeframe for the items is 'during the past week'. The total score per scale is converted to a score ranging from 0 to 100. Higher scores indicate less disability. Both the primary English MHQ and the official Dutch translation have good psychometric properties [8, 33-38].

Table 2. Legacy instruments

DASH	30 items (addressed to disabilities and symptoms in musculoskeletal disorders of the upper limbs). Timeframe: during the last week. Six different 5-point Likert response scales: • No difficulty/Mild difficulty/Moderate difficulty/Severe difficulty/Unable • Not at all/Slightly/Moderately/Quite a bit/Extremely • Not limited at all/Slightly limited/Moderately limited/Very limited/Unable • None/Mild/Moderate/Severe/Extreme • No difficulty/Mild difficulty/Moderate difficulty/Severe difficulty/So much difficulty that I can't sleep • Strongly disagree/Disagree/Neither agree or disagree/Agree/Strongly agree. Higher scores imply more disability: 0 (no disability) to 100 (most severe disability).
PRWE	15 items (addressed to pain and function in patients with wrist fractures). The function subscale contains two sections; specific activities and usual activities. Timeframe: during the last week. Two different 11-point response scales: • Pain: 0 (no pain) to 10 (unbearable pain) • Function: 0 (no disability) to 10 (most disability) Higher scores imply worse outcome: 0 (no disability and no pain) to 100 (most disability and unbearable pain).
MHQ-ADL	17 items (addressed to activities of daily living). Timeframe: during the last week. One 5-point Likert response scale: • Not difficult at all/A little difficult/Somewhat difficult/Moderately difficult/Very difficult. Higher scores imply less disability: 0 (Very difficult to do) to 100 (not difficult to do at all).

DASH=Disability of Arm, Shoulder and Hand, MHQ-ADL=Michigan Hand Questionnaire-Activities of Daily Living subscale

Analysis

Sample size. There are varying views and guidelines to determine the sample size for validating questionnaires.[39] The required sample size for Confirmatory Factor Analysis (CFA) was estimated as at least 300 participants, based on recommendations by Comrey and Lee [40].

Structural validity

Structural validity measures the degree to which the scores of a health-related PRO instrument are an adequate reflection of the dimensionality of the construct to be measured [41]. In this study, the structural validity of the DF-PROMIS-UE v2.0 item bank was assessed by confirmatory factor analyses (CFA). A single factor model of the DF-PROMIS-UE v2.0 item bank was tested. Because the item bank is supposed to measure one construct (upper extremity physical function), we expect that all items load on a single factor. Unidimensionality was examined by CFA on the polychoric correlation matrix with Weighted Least Squares with Mean and Variance adjustment (WLSMV) estimation. The Comparative Fit Index (CFI), Tucker Lewis Index (TLI), Root Means Square Error of Approximation (RMSEA), and Standardized Root Mean Residual (SRMR) evaluate model fit. We report scaled fit indices, which are considered more exact than unscaled indices [42]. Following the PROMIS analysis plan [23] and recommendations by Hu and Bentler [43] we considered sufficient evidence for unidimensionality and thus adequate model fit if CFI was close to 0.95 or higher, a TLI close to 0.95 or higher, a RMSEA close to 0.06 or less and a SRMR close to 0.08 or less.

If the model did not fit well, a bi-factor model was used to examine if the scale is unidimensional enough for future IRT analyses. To evaluate the influence of multidimensionality a bi-factor model was fitted, and omega-H and Explained Common Variance (ECV) were calculated. A high omega H value indicates that a composite score is reflected by a single common source, for example one common factor underlies item responses [44, 45]. The Explained Common Variance (ECV) was calculated, which is the ratio of the variance explained by the general factor, divided by the variance explained by the general factor and the group factors. A high coefficient omega (>0.80)[44] and a high ECV (>0.60) [45] indicate that the risk of biased parameters when fitting multidimensional data into a unidimensional model is low.

In addition, an Exploratory Factor Analysis (EFA) with WLSMV estimation procedures using the R package Psych (version 1.7.5) was performed [46]. The first factor in EFA should account for at least 20% of the variability, and the ratio of the variance explained by the first to the second factor needs to be greater than four [23, 47].

Factor loadings were calculated to give a representation of the relationship of each item to the underlying factor. The factor loading is the correlation between the observed score and the latent score. Factor loadings had to be higher than the criterion of >0.50 [40, 48, 49].

Internal consistency

Internal consistency measures the degree of the interrelatedness among the items [41, 50]. The internal consistency of the full item bank as well as the standard 7-item Short Form was determined after conducting a factor analysis. Internal consistency was assessed by calculating Cronbach's alpha. A Cronbach's alpha of >0.70 was considered sufficient evidence for internal consistency [51, 52].

Construct validity

T-scores were calculated for the DF-PROMIS-UE v2.0 item bank, based on response pattern scoring using the US item parameters. The T-scores were correlated (Pearson correlations) to the scores of the legacy instruments. For assessing convergent validity, we hypothesized that the DF-PROMIS-UE v2.0 item bank score has a:

- Hypothesis 1: Strong negative correlation ($r \geq -0.50$) with the DASH, given the fact that both instruments are supposed to measure related constructs (UE related physical function and UE physical function and symptoms).
- Hypothesis 2: Moderately strong negative correlation ($-0.50 \leq r \leq -0.30$) with the PRWE function, because both instruments are supposed to measure hand and wrist related activities and function. Because of this expected correlation, we hypothesized that the PRWE function is stronger correlated to the Dutch-Flemish PROMIS UE v2.0 item bank than PRWE pain.
- Hypothesis 3: Moderately strong positive correlation ($0.30 \leq r \leq 0.50$) with the MHQ-ADL, because both instruments are supposed to measure related constructs of upper extremity related physical function and hand related daily activities.

Construct validity was considered sufficient if at least 75% of the correlations were as expected [52].

RESULTS

A total of 524 patients with upper extremity injuries were approached (Figure 1). A total amount of 405 patients were eligible to participate in this study and gave informed consent, of which 303 (74.8%) completed the online questionnaires (Figure 1). There were no missing values in the completed questionnaires.

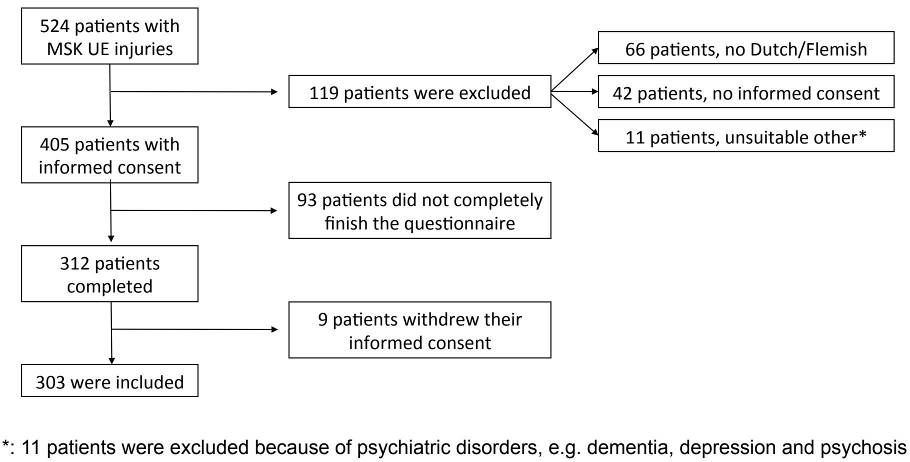

Figure 1. Sample size, inclusions and exclusions

Demographic and clinical characteristics are presented in Table 3. Of the 303 included patients, 159 were male (52%) and 144 females (48%). The mean age was 50.1 years (SD= 17.5), ranging from 18 until 93 years. An amount of 276 (91%) patients were born in the Netherlands.

Regarding educational levels, 68% had at least a high school degree. The largest group (122 patients, 40%) had achieved a college degree and only 7 patients (2%) had only a primary school degree. After injury, 174 patients (57%) were able to remain their job without major adjustments. About 10% declared to be unemployed, and 11% was reported ill, due to their injury. Of the total group, 50 patients (17%) had a pending (injury)claim (Table 3). Most included patients had injuries with an acute or semi acute onset, with a follow-up duration of 1 until 4 months in 30%.

Most reported physical injuries were fractures, tendon injuries and muscle injuries. Of all injuries, 72% were fractures, mainly distal radius fractures (16%), clavicle fractures (15%) and proximal humeral fractures (12%) (Figure 2). Conservative treatment was maintained in 217 injured patients (72%). The other 86 patients (28%) needed surgical treatment (Table 3).

Table 3. Demographic & Clinical characteristics (N=303)

Characteristics			
Age (years)	Mean (SD)	50.07	17.5
Range		18-93	
		N	**%**
Gender			
Male		159	52
Female		144	48
Employment status			
Fulltime		141	47
Part-time		55	18
Student		20	7
Unpaid, volunteer or household		13	4
Retired		49	16
Unemployed		6	2
Other		19	6
Injury influence on employment status			
Remained the same, no large influence		174	57
Modified work, function remained		59	20
Other function		7	2
Unemployed		31	10
Called in sick at work		32	11
Current compensation claim			
Yes		50	17
No		253	83
Dominant hand			
Left-handed		41	14
Right-handed		258	85
Ambidextrous		4	1
Treatment			
Conservative		217	72
Surgery		86	28

N=number of patients, SD=Standard Deviation, %=percentage

Statistical analysis

Structural validity. With CFA we found a CFI of 0.94, a TLI of 0.93, a RMSEA of 0.10 and a SRMR of 0.09, which was near the reference criteria [23, 43-47]. The factor loadings for this model were 0.73 or higher (mean 0.83, and range 0.73 to 0.94), which were all above the criteria of >0.50 [40, 48]. A bi-factor model was investigated, to examine if the scale is unidimensional enough for future IRT analyses. Omega-H and ECV were 0.79 and 0.67 respectively, which indicated sufficient unidimensionality. In addition, in EFA three factors with eigenvalues greater than 1 were identified. The eigenvalue of the first factor was 29.6, the eigenvalue of the second and third factors were 2.7 and 2.3, respectively. The ratio of the first to the second factor was 11.0, which is larger than de criterion of 4.

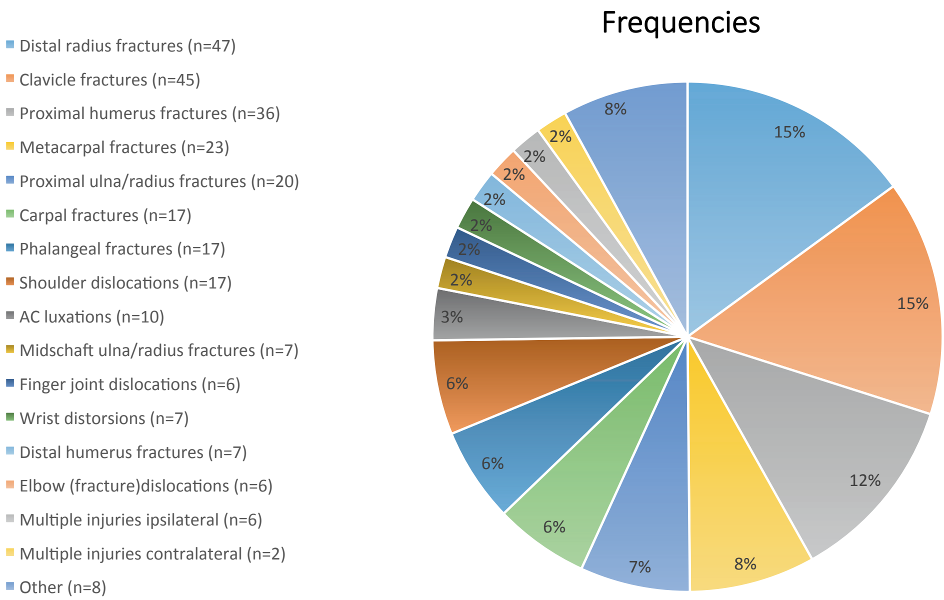

Figure 2. Types of injury, pie-chart ratio

Internal consistency. Cronbach's alpha for the full DF-PROMIS-UE v2.0 item bank was 0.98, which is above the criterion of >0.70 [51]. The Cronbach's alpha of the PROMIS UE Short Form 7a was 0.90, which is also above the criterion of >0.70.

Construct validity. Mean (SD) T-scores for the DF-PROMIS-UE v2.0 were 33.4 (9.1), for the DASH 35.5 (22.1), for the PRWE function 26.0 (15.8), for the PRWE pain 20.9 (14.0), for the PRWE total 46.9 (27.1) and for the MHQ-ADL total (per injured side) 57.4 (34.8) (Table 4). The correlations of T-scores the DF-PROMIS-UE v2.0 item bank with the T-scores of the DASH, PRWE function, PRWE pain, PRWE total and MHQ-ADL were, -0.84, -0.75, -0.59, -0.74 and 0.73, respectively, with all *p*-values <0.001. Only the correlation of the DF-PROMIS-UE v2.0 item bank with the DASH met our hypothesis, a strong negative correlation. The correlations between the DF-PROMIS-UE v2.0 item bank with PRWE function, PRWE pain, PRWE total and MHQ-ADL were higher than expected.

Table 4. T-scores (N=303)

	Mean	SD
DF-PROMIS-UE v2.0	33.4	9.1
DASH	35.5	22.1
PRWE Function	26.0	15.8
PRWE Pain	20.9	14.0
PRWE Total	46.9	27.1
MHQ-ADL*	57.4	34.8

*: MHQ-ADL total scores per injured side (right sided, left sided or both sides injured), SD=Standard Deviation

DISCUSSION

The aim of this study was to examine the structural validity, internal consistency, and construct validity of the DF-PROMIS-UE v2.0 item bank, in order to make it applicable in the outpatient clinic setting. The results show that the DF-PROMIS-UE v2.0 item bank measures a unidimensional trait and has sufficient structural validity, internal consistency, and construct validity.

The CFA analyses showed a CFI and TLI of 0.94 and 0.93, which are lower than, but near the criterion of >0.95. A RMSEA of 0.10 and a SRMR of 0.09 were found, which are also near the criteria of <0.06 and <0.08 respectively. The RMSEA was higher than the maximum criterion of <0.06 [43]. Inconsistent results have been found for other versions of the PROMIS Physical Function item bank. Rose et al. reported a RMSEA of about 0.08 for subsets of items from the original English PF v1.2 item bank [16]. The Dutch-Flemish PROMIS Physical Function v1.2 item bank showed a RMSEA of 0.122 [19] and 0.045 [20] in previous studies, respectively. For the Spanish population in the US, a RMSEA of 0.052 was found for the PROMIS Physical Function v1.2 item bank [53]. The RMSEA was not reported for the US PROMIS UE population [54, 55]. It has been suggested that traditional cut-offs and standards for CFA fit statistics are not suitable to establish unidimensionality of item banks measuring health concepts [56] and that the RMSEA is sensitive to model complexity (number of estimated parameters) and skewed data distributions [56], the latter being the case in health concepts. Reise *et al.* have stated that the RMSEA statistic is problematic for assessing unidimensionality of health concepts, and considered the SRMR more promising to determine whether a scale is 'unidimensional enough' [45]. The SRMR was 0.09 in our study, slightly higher than the criterion of 0.80. None of the studies on the US PROMIS UE [54, 55] or Spanish PROMIS UE item bank [53] reported the SRMR.

All factor loadings for this model were above the criterion of at least 0.50 or higher, with a smallest factor loading of 0.73 [40]. Paz *et al.* found factor loadings all above the criterion of 0.70 for the Spanish PROMIS Physical Function v1.2 item bank, except for 2 items (PFC7 and PFA19) but these items are not included in the UE item bank [53]. Hays *et al.* found PROMIS UE factor loadings all above 0.70 as well in a US population, with a smallest factor loading of 0.85 [57]. These results support the hypothesis of unidimensionality of the PROMIS UE v2.0 item bank. Other authors have recommended fitting a bi-factor model and consider the Omega H and ECG when the RMSEA does not fit the criterion of <0.06 [45, 53-55]. The omega-H in our study was 0.79, which was just beneath, but very close to the criterion of >0.80, which suggests that a composite score is reflected by a single common source. The ECV was 0.67, which is higher than the criterion of >0.60. Together this suggests that the risk of biased parameters when fitting multidimensional data into a unidimensional model was low.

Finally, in EFA analyses the first factor accounted for more than 20% of the variability and the ratio of the variance explained by the first to the second factor was 11.0. All these results together suggest enough evidence for unidimensionality of the DF-PROMIS-UE v2.0 item bank.

Internal consistency. Evidence for sufficient internal consistency was indicated by a Cronbach's alpha for the entire item bank of 0.98, which is higher than the criterion of >0.70 [41, 50, 51]. Kaat *et al.* found an average marginal reliability of 0.90 for the PROMIS UE item bank [54]. Beckman *et al.* and Paz *et al.* both found a Cronbach's alpha of 0.99 for the PROMIS UE item bank [21, 53]. This suggests that the internal consistency found in this study, was comparable to the internal consistency found in previous studies. The Cronbach's alpha of the entire item bank might be this high because the scale includes 46 items. A very high Cronbach's alpha might suggest redundancy of items, but since the entire item bank will not be used in clinical practice, this seems not to be problem. The Cronbach's alpha of the PROMIS UE short form 7a is possibly more relevant, because this short form will be used in clinical practice, instead of the entire item bank. The Cronbach's alpha of the PROMIS UE short form 7a was 0.90. Chung *et al.* found a Cronbach's alpha of 0.97 for the MHQ-ADL [8]. For the DASH a Cronbach's alpha of 0.95 was found by van Eck *et al* [31]. Cronbach's alpha was also calculated by El Moumni *et al.* for the PRWE total, PRWE pain and PRWE function, which was 0.97, 0.94 and 0.96, respectively [3]. The Cronbach alpha's found for the DASH, PRWE and MHQ-ADL, were all relatively high, but comparable in terms of meeting the criterion of > 0.70 to the results found for the DF-PROMIS-UE v2.0 short form 7a in this study. This suggests that evidence for the internal consistency was sufficient, and comparable to the legacy instruments.

Construct validity. Our first hypothesis regarding the correlation between the DF-PROMIS-UE v2.0 item bank and the DASH questionnaire was met; there was a strong negative correlation (-0.84). This result was comparable to results from Beckmann *et al.* [21]. They found a correlation of -0.80 between the US PROMIS UE v2.0 item bank and the DASH [21]. Kaat *et al.* found a correlation of -0.82, and Doring *et al.* found a correlation of -0.81 between the PROMIS UE v2.0 item bank and the Quick DASH [54, 58]. Overall, this suggests that the PROMIS UE v2.0 item bank and DASH measure similar constructs.

Our second hypothesis regarding the correlation between the DF-PROMIS-UE v2.0 item bank and the PRWE total questionnaire was not met. We found a strong negative correlation (-0.74), instead of the expected moderately strong negative correlation ($-0.50 \leq r \leq -0.30$). For the PRWE pain and PRWE function subscales, correlations of -0.59 and -0.75 were found, supporting the hypothesis that the DF-PROMIS-UE v2.0 item bank has a stronger correlation with the PRWE function subscale than with the PRWE pain subscale.

Our third hypothesis regarding the correlation between the DF-PROMIS-UE v2.0 item bank and the MHQ-ADL was not met as well. A moderately strong positive correlation was expected ($0.30 \leq r \leq 0.50$), though we found a strong positive correlation (0.73). Apparently, the DF-PROMIS-UE v2.0 item bank has more content overlap with the PRWE and MHQ-ADL than we expected. This could actually be considered a positive finding because it shows that the DF-PROMIS-UE v2.0 item bank is capable of measuring upper extremity related physical function, as well as hand- and wrist related function, comparable to the DASH, PRWE and MHQ-ADL.

Strengths and weaknesses

A sample size of at least 300 participants was achieved, meeting the recommendations by Comrey and Lee [40]. Patients of all ages and with all kind of upper extremity injuries were included, which supports the representativeness of the study population. The main experienced upper extremity injuries were distal radius fractures, clavicle fractures and proximal humeral fractures. A study by Beerekamp *et al.*, performed in the Netherlands, estimated the prevalence of extremity fractures in general [59]. The most commonly reported fractures, were hand and finger fractures (N=34.144), wrist fractures (N=25.432) and clavicle and shoulder fractures (N= 13.264) [59]. Hand and finger fractures included carpal, metacarpal and phalangeal fractures together [59]. In our sample the sum of these injuries was 20% (N=57). These results were comparable to the results of the Beerekamp sample.

This study was conducted according to the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) Risk of Bias-checklist. Adequate study design for cross-sectional validity and construct validity were ensured [51, 60]. Besides, the international PROMIS guidelines for instrument development and validation were followed [25].

Because the hospital the patients were recruited in is a level 1 trauma centre, patients with severe and multiple injuries (polytrauma patients) are overrepresented. In community hospitals, there are less severely injured patients, the mono-trauma patients. These differences can cause bias in the sample and have effect on the representativeness of the study sample. Severely injured patients, often have multiple fractures and corresponding soft-tissue injuries, which has a negative effect on outcome. This might explain a higher amount of severely injured patients with a higher amount of worse outcome in level 1 traumacenters. The implementation of the DF-PROMIS-UE v2.0 in outpatient clinical environment might be challenging, due to the need of mobile devices and accessibility to internet. However, almost all patients own a mobile device and internet-based PROs have been implemented worldwide. We therefore think that once an internet-based questionnaire including the DF-PROMIS-UE v2.0 has been implemented in your outpatient clinic, it can decrease the burden for the patient and improve interpretation of outcome tremendously.

Clinical interpretation

For daily practice, the DF-PROMIS-UE v2.0 item bank is a suitable instrument to measure rehabilitation progress, in comparison with the legacy instruments (DASH, PRWE and MHQ-ADL). The benefit of the DF-PROMIS-UE v2.0 item bank is that it can be applied across patient populations, enabling comparison of scores, and it can be used as CAT, which reduces response burden for patients and increases the usability of the DF-PROMIS-UE v2.0 item bank in daily practice. Therefore, we recommend future studies to consider using PROMIS instead of the legacy instruments.

Conclusions

This study showed that the DF-PROMIS-UE v2.0 item bank measures a unidimensional trait and sufficient structural validity, internal consistency and construct validity were found. Further studies should assess further validation and calibration by IRT analysis, as well as other measurement properties, such as test-retest reliability, measurement error, and responsiveness. After successful IRT analysis, the DF-PROMIS-UE v2.0 CAT will be operable to use.

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CHAPTER 8

Grade response model fit, measurement invariance and (comparative) precision of the Dutch-Flemish PROMIS® Upper Extremity v2.0 item bank in patients with upper extremity disorders

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ABSTRACT

Introduction. The Dutch-Flemish PROMIS® Upper Extremity (DF-PROMIS-UE) v2.0 item bank was recently developed using Item Response Theory (IRT). Unknown for this bank are: (1) if it is legitimate to calculate IRT-based scores for short forms and Computerized Adaptive Tests (CATs), which requires that the items meet the assumptions of and fit the IRT-model (Graded Response Model [GRM]);(2) if it is legitimate to compare (sub)groups of patients using this measure, which requires measurement invariance; and (3) the precision of the estimated patients' scores for patients with different levels of functioning and compared to legacy measures. Aims were to evaluate (1) the assumptions of and fit to the GRM, (2) measurement invariance and (3) (comparative) precision of the DF-PROMIS-UE v2.0.

Methods. Cross-sectional data were collected in Dutch patients with upper extremity disorders. Assessed were IRT-assumptions (unidimensionality [bi-factor analysis], local independence [residual correlations], monotonicity [coefficient H]), GRM item fit, measurement invariance (absence of Differential Item Functioning [DIF] due to age, gender, center, duration, and location of complaints) and precision (standard error of IRT-based scores across levels of functioning). To study measurement invariance for language [Dutch vs. English], additional US data were used. Legacy instruments were the Disability of the Arm, Shoulder and Hand (DASH), the QuickDASH and the Michigan Hand Questionnaire (MHQ).

Results. In total 521 Dutch (mean age±SD=51±17years, 49% female) and 246 US patients (mean age±SD=48±14years, 69% female) participated. The DF-PROMIS-UE v2.0 item bank was sufficiently unidimensional (Omega-H=0.80, Explained Common Variance=0.68), had negligible local dependence (3.3% item-pairs correlations>0.20), good monotonicity (H=0.63), good GRM fit (no misfitting items) and demonstrated sufficient measurement invariance. Precise estimates (Standard Error<3.2) were obtained for most patients (7-item short form, 88.5%; standard CAT, 91.3%; and, fixed 7-item CAT, 87.6%). The DASH displayed better reliability, though it was considerably longer, than the DF-PROMIS-UE short form and standard CAT, the QuickDASH displayed comparable reliability. The MHQ-ADL displayed better reliability than the DF-PROMIS-UE short form and standard CAT for T-scores between 28-50. For patients with low function, the DF-PROMIS-UE measures performed better.

Conclusions. The DF-PROMIS-UE v2.0 item bank showed sufficient psychometric properties in Dutch patients with UE disorders.

INTRODUCTION

Upper extremity (UE) disorders impact on health care, society and the lives of patients. For instance in the field of orthopaedic and trauma surgery, UE disorders account for a large proportion of attendances to the Emergency Department with highest incidences in young patients and elderly females [1]. Total annual costs for all acute and chronic disorders of the upper extremity are reported to be 290 million euro, of which wrist fractures are the most expensive injuries (83 million euro) due to high incidence, whereas upper arm fractures are most expensive per case (4440 euro) [1]. In addition, these disorders cause considerable losses in working days and productivity [2]. The disability caused by upper extremity disorders significantly reduces physical, mental, and social health [2].

Patient reported outcomes (PROs), consisting of validated questionnaires, are increasingly used in daily clinical practice to assess the impact of acute and chronic UE disorders on the lives of patients. In the past outcomes following these disorders were objectified using clinical measurements such as grip strength, range of motion, and radiological parameters. Nowadays the patient perspective on these outcomes is becoming more important. This may include the impact on physical health (e.g., physical functioning, pain intensity and interference), mental health (e.g., depression), and social health (e.g., ability to participate in social roles and activities).

The use of PROs in daily clinical practice and for research purposes is not without problems. Many different PROs have been developed and are being used in patients with UE disorders, including the Disability of the Arm, Shoulder and Hand (DASH) questionnaire [3], the QuickDASH [4], the Patient-Rated Wrist Evaluation (PRWE) [5], and the Michigan Hand Questionnaire (MHQ) [6]. Variation exists in their psychometric properties [7-10]. In addition, completing PROs is time consuming for patients. Finally, the interpretation of the PRO scores is hampered by the variability of conditions the PROs are applied to [8] and varies between them.

The Patient-Reported Outcomes Measurement Information System (PROMIS®) might offer a solution for some of the problems related to the use of traditional PROs. The National Institutes of Health PROMIS® initiative has developed a new assessment system for measuring patient-reported health. The goal was to improve measurement quality and comparability of PROs and reduce patients' burden. Item banks were developed and validated for measuring specific symptoms and health status domains [11,12]. An item bank is a universal (non-disease specific) applicable set of items (questions) with responses (answers) that all measure the same domain (construct or concept) [13]. The items of a bank are calibrated on a scale, using a modern psychometric technique, called Item Response Theory (IRT) modelling. In this way, people and items are located on the same scale (ruler or metric) according to their "difficulty". For PROMIS, the score is expressed as a T-score, which is a standardized score, with 50 currently representing the average score of the US general population, with a standard deviation of 10. IRT-based item banks enable the use of short forms (fixed subsets of items from the item bank) and Computerized Adaptive Testing (CAT). CAT uses an algorithm that selects the most informative items from the item bank, based on the individual's response to previously administered items. In this way, high measurement precision can be obtained with low respondent burden [11,14].

PROMIS included an item bank that measures UE-related physical functioning and this bank has recently been updated, from v1.2 to v2.0, to measure a wider range of upper extremity functioning and showed higher precision when used in patients with UE disorders [15]. The v2.0 item bank was translated into Dutch-Flemish (DF-PROMIS-UE v2.0) and some of the psychometric properties of this bank have been studied in patients with UE disorders from a general [16] and an academic hospital [17]. Evidence was found for the following psychometric properties: internal consistency [17], structural validity [17], construct validity [16,17] and cross-cultural validity [16]. In addition, absence of floor and ceiling effects in the full bank and the 7-item short form was shown [16].

Some other important psychometric properties of the DF-PROMIS-UE v2.0 item bank still need to be evaluated. Unknown for the DF-PROMIS-UE v2.0 bank are: (1) if it is legitimate to calculate IRT-based scores for short forms and Computerizes Adaptive Tests (CATs), which requires that the items meet the assumptions of and fit to the IRT-model (in this case the Graded Response Model [GRM]);(2) if it is legitimate to compare (sub)groups of patients using the measure at issue, which requires measurement invariance; and (3) the precision of the estimated patients' scores for patients with different levels of functioning and compared to legacy measures. Therefore, the aims of this study were to evaluate (1) the assumptions of and fit to the GRM, (2) measurement invariance and (3) (comparative) precision of the DF-PROMIS-UE v2.0 item bank in patients with UE disorders in comparison to legacy instruments Disability of Arm Shoulder and Hand (DASH) questionnaire, QuickDASH and Michigan Hand Questionnaire (MHQ).

METHODS

Participants

Patients visiting the outpatient department of trauma surgery at a level 1 traumacenter or the outpatient department of orthopaedic surgery at a level 2 traumacenter, between February 2018 and August 2018, were invited to participate. Patients were eligible if they were 18 years or older, had an UE disorder, were able to read Dutch and provided informed consent. We deemed a sample of at least 500 patients sufficient for item parameter estimation [18]. To study measurement invariance for language, we used additional data of US patients from an online panel, aged 18 years or older, who endorsed having some difficulty due to UE pain or function [15,19].

Measures

Besides demographic and disease specific questions, the questionnaire included the full DF-PROMIS-UE v2.0 item bank. In addition, the questionnaire contained 3 disease-specific legacy instruments: the DASH, the QuickDASH and the MHQ (Table 1).

The DF-PROMIS-UE v2.0 item bank contains 46 items addressing upper extremity function. There are two different 5-point Likert response scales: 1) Unable to do/With much difficulty/ With some difficulty/With a little difficulty/Without any difficulty; 2) Cannot do/Quite a lot/ Somewhat/Very little/Not at all. There is no timeframe for the items, but current status is inferred. Higher scores indicate better function. A 7-item short form was developed. In addition, the item bank can be used as CAT. The total score of the DF-PROMIS-UE v2.0 item bank, short form or CAT is not a sum or total score, but a weighted score, based on the underlying IRT-model, taking the difficulty of the items into account. All scores are expressed as a T-score, which is a standardized score, with 50 currently representing the average score of the US general population, with a standard deviation of 10, and higher scores indicate more of the domain at issue, in this case better UE-related physical functioning.

The DASH questionnaire contains 30 items, specifically addressed to physical function and symptoms in musculoskeletal disorders of the upper extremity (Table 1) [3]. Both the original English DASH and the official Dutch translation were found to have sufficient psychometric properties[20-22].

The QuickDASH is an 11-item shortened version of the DASH (Table 1). Using conceptual methods these eleven items were selected from the total DASH questionnaire based on the criteria: 1) number of items with > 40% in one response category, 2) Cronbach's alpha > 0.90 and 3) highest correlation with the 30-item DASH and with other markers of physical function and severity of problem. The QuickDASH has sufficient psychometric properties[4].

The MHQ is a hand-specific instrument that measures several domains and is applicable to patients with conditions of, or injury to, the hand and wrist (Table 1) [6]. The MHQ contains six distinct subscales. In this study, we used the MHQ subscale Activities of Daily Living (MHQ-ADL), which assesses difficulty in performing daily activities for the right hand (5 items), for the left hand (5 items) and both hands (7 items). We used the 7 items referring to both hands because this corresponds most with the generic PROMIS items. The psychometric properties of the MHQ score were found to be sufficient [6,23-27].

Table 1. Legacy instruments

DASH	30 items (addressed to disabilities and symptoms in musculoskeletal disorders of the upper limbs). Timeframe: during the last week. Six different 5-point Likert response scales: • No difficulty/Mild difficulty/Moderate difficulty/Severe difficulty/Unable • Not at all/Slightly/Moderately/Quite a bit/Extremely • Not limited at all/Slightly limited/Moderately limited/Very limited/Unable • None/Mild/Moderate/Severe/Extreme • No difficulty/Mild difficulty/Moderate difficulty/Severe difficulty/So much difficulty that I can't sleep • Strongly disagree/Disagree/Neither agree or disagree/Agree/Strongly agree. Higher scores imply more disability: 0 (no disability) to 100 (most severe disability).
QuickDASH	11 items (addressed to disabilities and symptoms in musculoskeletal disorders of the upper limbs). Timeframe: during the last week. Two different 11-point response scales: • Pain: 0 (no pain) to 10 (unbearable pain) • Function: 0 (no disability) to 10 (most disability) Higher scores imply more disability: 0 (no disability) to 100 (most severe disability).
MHQ-ADL	17 items (addressed to activities of daily living). Timeframe: during the last week. One 5-point Likert response scale: • Not difficult at all/A little difficult/Somewhat difficult/Moderately difficult/Very difficult. Higher scores imply less disability: 0 (Very difficult to do) to 100 (not difficult to do at all).

DASH=Disability of Arm, Shoulder and Hand, MHQ-ADL=Michigan Hand Questionnaire-Activities of Daily Living subscale

Procedures

The study was approved by the local medical ethics committees of the participating hospitals. Consenting patients were requested to complete all 46 items of the DF-PROMIS-UE v2.0 item bank through an online survey and, only if preferred, using a paper version of the questionnaire. In addition, patients completed general questions regarding age, gender, education and ethnicity. Also questions regarding type of injury and duration of complaints were included. In addition, the DASH, which encompasses the QuickDASH, and the MHQ were completed.

Statistical analysis

IRT-model assumptions and fit

The psychometric analyses were conducted using the original PROMIS analysis plan[14]. For an item bank it is important to know if it is legitimate to calculate IRT-based scores for short forms and CATs. This requires, firstly, that the items meet the three assumptions of an IRT-model and, secondly, fit to the IRT-model at issue. An IRT-model requires that the following three assumptions are met: unidimensionality, local independence, and monotonicity [14].

Studying the first IRT-assumption, unidimensionality, addresses the research question whether the items assessed one construct, in this case UE-related physical function. Unidimensionality was evaluated using multiple methods:

a. Exploratory Factor Analysis (EFA). EFA was carried out on the polychoric correlation matrix with Weighted Least Squares with Mean and Variance adjustment (WLSMV) estimation procedures using the R package Psych (version 1.7.5) [18]. Unidimensionality was considered sufficient when the first factor accounts for at least 20% of the variability and when the ratio of the variance explained by the first to the second factor is greater than 4 [14].
b. Confirmatory Factor Analyses (CFA). The CFA was conducted on the polychoric correlation matrix with WLSMV estimation, using the R package LAVAAN (version 0.5-23.1097) [28]. Fit of the unidimensional model was evaluated using the following criteria: Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Root Means Square Error of Approximation (RMSEA) and Standardized Root Mean Residual (SRMR) [28]. We reported scaled fit indices, which are considered more exact than unscaled indices. Sufficient evidence for unidimensionality and thus adequate model fit was considered if CFI > 0.95, TLI > 0.95, RMSEA < 0.06 and a SRMR < 0.08 [14,29].
c. Exploratory bi-factor analysis. Bi-factor analysis evaluates, when multidimensionality is present, the impact of multidimensionality. Exploratory bi-factor analysis was conducted using the R package Psych (version 1.7.5). Criteria were: omega H and Explained Common Variance (ECV). Coefficient omega H >0.80 [30] and ECV >0.60 [31] indicates that the risk of biased parameters, when fitting multidimensionality data into a unidimensional model, is low.

Studying the second IRT-assumption, local independence, addresses the research question whether the items are only related to the construct (the dominant factor) being measured and not to other constructs (any other factors). This implies that, after controlling for the dominant factor, there should be no significant covariance between item responses. Local independence was evaluated by examining the residual correlation matrix resulting from the single factor CFA. Residual correlations ≥ 0.2 were considered as indicators of possible local independence [14]. Afterwards, the impact of the items marked as possible local independent on the item parameters, was evaluated. This was evaluated by removing the locally dependent items one by one, and examining changes in the IRT parameters of the remaining items [14].

Studying the third IRT-assumption, monotonicity, addresses the research question whether the probability of an affirmative response to the items increases with increasing levels of the underlying construct. This implies, e.g., in case the item responses "Unable to do/With much difficulty/With some difficulty/With a little difficulty/Without any difficulty", that the probability of endorsing a higher item response category, e.g., choosing "Without any difficulty" instead of "With a little difficulty", should increase with increasing levels of the underlying construct, in this case the UE-related physical functioning. Monotonicity was evaluated by fitting a non-parametric IRT model, using Mokken scaling in the R package Mokken (version 2.8.4) [32,33]. We evaluated the fit of the model by calculating the scalability coefficient H per item and for the total scale. We considered monotonicity acceptable if the scalability coefficients for the items were ≥ 0.30 and for the total scale ≥ 0.50 [32].

After evaluation of the IRT-assumptions, the IRT-model at issue, in this case the logistic Graded Response Model (GRM) which is an IRT-model for ordinal data, was fit to the item response data. The GRM model yields two item parameters estimates: the item threshold and the item slope [34]. Item threshold parameters locate items along the scale (i.e. the construct of interest) [34]. The item slope parameter refers to the discriminative ability of the items, with higher slope values indicating a stronger relationship to the construct of interest[34]. For items with five response categories, four item thresholds were estimated. To assess the fit of the GRM we used the R-package Mirt (version 3.3.2) [35]. To assess the degree to which possible misfit affects the IRT-model, a generalization of Orlando and Thissen's S-X^2 for polytomous data was used [36]. These statistics compare the observed and expected response frequencies under the estimated IRT model and quantifies the differences between the observed and expected response frequencies. Items with a S-X^2 p-value ≤ 0.001 demonstrate poor fit [14,37].

Measurement invariance

Evaluating measurement invariance addresses the research question whether it is legitimate to compare (sub)groups of patients using the measure at issue. Item parameters should be equivalent between (sub)groups, e.g., age or gender groups, implying that there should be absence of Differential Item Functioning (DIF). DIF analyses are used to examine if people from different (sub)groups, e.g. males versus females, with the same level of the construct, e.g. the same level of UE-related physical functioning, have different probabilities of giving a certain response to an item [14,34,38]. Uniform DIF exists when the DIF is consistent, with the same magnitude of DIF across the entire range of the construct [14,34,38]. In this case the item location parameters differ between the (sub)groups. Non-uniform DIF exists when the magnitude or direction of DIF differs across the construct. In this case the item discrimination parameters differ between the (sub)groups. DIF was evaluated with use of the R package Lordif (version 0.3-3), using ordinal logistic regression models with a McFadden's pseudo R^2 change of 2% as critical value [14,39,40]. DIF was evaluated for age (median split: <53 years versus ≥ 53 years), gender, duration of complaints (<6 months versus ≥6 months), primary location of complaints (hand/wrist versus arm/shoulder). Regarding location of complaints, patients were able to report on multiple areas. For the DIF analysis regarding location of complaints we used patients who reported either pain in shoulder/arm or hand/wrist only. Measurement invariance for language is a key aspect of cross-cultural validity and was addressed by a DIF analysis for language (Dutch-Flemish versus American-English). In the US dataset some response categories had insufficient responses for analysis and these categories had to be collapsed. In order to compare our population with the US population, scores on the response categories "without much difficulty" and "unable to do" were therefore also collapsed for 8 items (PFA43r1, PFB16r1, PFB19r1, PFB20r1, PFB21r1, PFB23r1, PFB31r1, and PFB37r1). For item PFB15r1 the response categories 'with some difficulty', 'without much difficulty' and 'unable to do' were collapsed, according to the US PROMIS convention [41].

Precision

Measurement precision (reliability) is conceptualized within IRT as "'information". In the context of IRT the measurement precision can differ across levels of the measured construct (θ = Theta). The relationship between information (I) and standard error (SE) is defined by the formula

SE (θ) = $1/\sqrt{I(\theta)}$, where SE is the standard error of the estimated θ, *I* is information and θ is the estimated level of the construct. For each patient, we calculated four T-scores: one based on all items of the item bank (using the US item parameters [42)], one based on the standard 7-item short form (using the US item parameters [42]) and two based on CAT simulations (using the item parameters obtained in our sample, and subsequently, we transformed thetas into T-scores on the US PROMIS metric using Stocking-Lord coefficients to make all scores comparable). In the first simulated CAT we used the standard PROMIS CAT stopping rules. The standard CAT stops if a SE of 3 on the T-score metric is reached, comparable to a reliability slightly higher than 0.90, or a maximum of 12 items has been administered. The recommended minimum of four items was not used because this could not be specified in the R-package at issue. In the second simulated CAT we administered a fixed number of seven items to compare the reliability of this CAT with the 7-item short form. In all simulations the starting item was the item with the highest information value for the average level of functioning in our study population (theta=0) [42]. We used the R-package catR (version 3.12) and *expected a posteriori* (EAP) estimations for the CAT simulations [18]. The SEs across T-scores for the entire item banks were plotted, for the standard 7-item short form, and for the two different CAT simulations. In addition, the distribution of T-scores in our population was plotted. This enables to relate the reliability of the item bank to the distribution of T-scores in this population.

To compare the precision of the DF-PROMIS-UE v2.0 item bank to the precision of the DASH, QuickDASH and the MHQ-ADL (comparative precision), we also fitted a GRM on these three legacy instruments. The scoring of the DASH and QuickDASH was reversed resulting in higher scores indicated better functioning, comparable to PROMIS. We plotted the Standard Errors (SEs) of the T-scores of the DASH, QuickDASH and MHQ-ADL in addition to the SEs of the T-scores of the DF-PROMIS-UE v2.0 short form and standard CAT.

In addition, relative efficiency was quantified per patient for each measure as Information ($(1/SE)^2$) divided by the number of items administered. Relative efficiency among the instruments was calculated as the mean efficiency of the PROMIS measures divided by the mean efficiency of the legacy measures. If the mean relative efficiency is larger than 1, the PROMIS measure is on average more efficient (more information per item) than the legacy instrument, but if it is less than 1, the legacy instrument is on average more efficient.

Table 2. Demographic and clinical characteristics of the Dutch and US samples

	Dutch sample (N=521)						US sample (N=246)	
	Level 1 center (N=303)		Level 2 center (N=218)		Total (N=521)			
Age, mean (SD)	50	(17)	53	(15)	51	(17)	48	(14)
Gender, N (%)								
Male	159	(53)	109	(50)	268	(51)	76	(31)
Female	144	(47)	109	(50)	253	(49)	170	(69)
Country of birth, N (%)								
Netherlands	276	(91)	161	(65)	437	(86)		
Other	27	(9)	44	(20)	71	(14)		
Missing	0	(0)	13	(15)	0	(0)		
Social status, N (%)								
Single	110	(36)	69	(32)	179	(34)		
Married/living together	155	(51)	127	(58)	282	(54)		
Living apart together	15	(5)	4	(2)	19	(4)		
Living with parents	16	(5)	6	(3)	22	(4)		
Other	7	(3)	12	(6)	19	(4)		
Educational level, N (%)								
< high school degree	34	(11)	40	(18)	74	(14)	6	(2)
High school degree	99	(33)	75	(34)	174	(33)	53	(22)
Some college	16	(5)	14	(6)	30	(6)	81	(33)
College degree	122	(40)	72	(33)	194	(37)	80	(32)
Advanced degree	32	(11)	17	(8)	49	(9)	26	(11)
Employment status, N (%)								
Full time	141	(47)	84	(39)	217	(43)		
Part time	55	(18)	40	(18)	93	(18)		
Student	20	(7)	5	(2)	25	(5)		
Unpaid/volunteer/household	13	(4)	18	(8)	31	(6)		
Retired	49	(16)	40	(18)	88	(17)		
Unemployed	6	(2)	10	(5)	14	(3)		
Other	19	(6)	21	(10)	40	(8)		
Duration of complaints, N (%)								
< 1 month	135	(45)	22	(10)	157	(30)		
1-3 months	39	(13)	22	(10)	61	(12)		
3-6 months	42	(14)	30	(14)	72	(14)		
< 6 months (DIF)	*216*	*(72)*	*74*	*(34)*	*290*	*(56)*		
6-12 months	20	(7)	36	(17)	56	(11)		
1-2 years	8	(3)	46	(21)	54	(10)		
2-5 years	2	(1)	31	(14)	33	(6)		
5 years	1	(0)	31	(14)	32	(6)		
≥ 6 months (DIF)	*31*	*(11)*	*144*	*(66)*	*175*	*(33)*		
Unknown/missing	56	(19)	0	(0)	56	(11)		

Table 2. Continued

	Dutch sample (N=521)						US sample (N=246)	
	Level 1 center (N=303)		**Level 2 center (N=218)**		**Total (N=521)**			
Location of pain[a], N (%)								
Shoulder(s)	137	(45)	190	(87)	318	(63)		
Arm(s)	125	(41)	142	(65)	259	(51)		
Shoulder/arm (DIF)[b]	*132*	*(44)*	*136*	*(62)*	*268*	*(80)*		
Hand(s)	105	(35)	59	(27)	161	(32)		
Finger(s)	64	(21)	49	(22)	112	(22)		
Hand/*wrist (DIF)*[b]	*62*	*(21)*	*7*	*(3)*	*69*	*(20)*		
DF-PROMIS-UE v2.0, mean (SD) T-scores	34.7	(3.6)	33.4	(9.1)	33.9	(8.9)	36.5	(7.0)
DASH, mean (SD) T-scores	35.6	(22.1)	36.5	(21.0)	35.9	(21.6)		
QuickDASH, mean (SD) T-scores	36.8	(22.1)	38.1	(21.8)	37.3	(22.0)		
MHQ-ADL, mean (SD) T-scores	61.4	(31.0)	74.5	(25.6)	66.7	(29.6)		

[a]Multiple answers were allowed, [b]For the DIF analysis regarding location of complaints only patients who reported either pain in shoulder/arm or hand/wrist were included

DASH=Disability of Arm, Shoulder and Hand, DF-PROMIS-UE v2.0= Dutch-Flemish translated version of the PROMIS Upper Extremity v2.0 item bank, DIF=differential item functioning, MHQ-ADL=Michigan Hand Questionnaire-Activities of Daily Living subscale, N=number of patients, SD=standard deviation, %=percentage

RESULTS

Of the 828 invited eligible patients (524 level 1 center and 304 level 2 center), 624 (75%) (405 level 1 center and 218 level 2 center) provided informed consent. Of these 624 consenting patients, 103 (all level 1) did not complete the questionnaire, even after two reminders by email. Of the remaining 521 (303 level 1 center and 218 level 2 center, total response rate 63%) patients, 515 fully completed the DF-PROMIS-UE v2.0 item bank. Most analyses were performed on 521 patients. The CAT simulations were performed on the 515 cases with complete DF-PROMIS-UE response data. The DIF analyses for location of complaints were based on 337 patients (268 patients who reported complaints in shoulder/arm only and 68 patients who reported complaints in the hand/wrist only).

Demographic and clinical characteristics

Demographic and clinical characteristics of the Dutch and US samples are summarized in Table 2. The mean age of the Dutch population was 51 years (SD 17) and 253 (49%) were female.

IRT-model assumptions and fit

The results of the psychometric analyses are summarized in Tables 3 and 4. The three IRT-assumptions were considered to be met and the items fitted to the GRM-model.

Unidimensionality. The results were considered showing enough evidence for unidimensionality (Omega-H=0.80, Explained Common Variance=0.68) (Table 3).

Local independence. Examination of the residual correlation matrix showed a small number of probable local dependent items. Thirty-four out of the 1058 item pairs (3.3%) with residual correlation > 0.20 were marked as possibly locally dependent. The top 3 item pairs with the greatest dependency were PFA48 (‘*Are you able to peel fruit?*’) and PFB28r1 (‘*Are you able to lift 10 pounds (5kg) above your shoulder?*’) with residual correlation of -0.31, PFA48 (‘*Are you able to peel fruit?*’) and PFB39r1 (‘*Are you able to reach and get down a 5 pound (2kg) object from above your head?*’) with residual correlation of -0.30 and PFB27 (‘*Are you able to tie a knot or a bow?*’) and PFB39r1 (‘*Are you able to reach and get down a 5 pound (2kg) object from above your head?*’) with residual correlation of -0.29. When local dependent items were removed, the maximum change in the item threshold parameters was 0.04 and in the item slope parameters was 0.15. Therefore, the impact of local dependence on item parameters was considered minimal.

Monotonicity. The scalability coefficients H_i of the items ranged from 0.55 (PFA17 *'Are you able to reach into a cupboard?'*) to 0.70 (PFM16 *'Are you able to pass a 20-pound (10kg) turkey or ham to other people at the table?'*) for the individual items (Table 4). The Mokken scalability coefficient H for the entire item bank was 0.63. Therefore, the DF-PROMIS-UE v2.0 items sufficiently met the monotonicity assumption.

GRM fit. There were no misfitting items (Table 4). The item thresholds ranged from -2.7 (PFA36 *'Are you able to put on and take off a coat or jacket?')* to 1.5 (PFM16 *'Are you able to pass a 20-pound (10kg) turkey or ham to other people at the table?').* The item discrimination parameters ranged from 1.7 to 3.6. The item with lowest discriminative ability was PFA17 (*'Are you able to reach into a cupboard?'*) and PFB30 (*'Are you able to open a new milk carton?')* was the item with highest discriminative ability.

Table 3. Results with respect to the IRT-model assumptions of the DF-PROMIS-UE v2.0 item bank

Analyses	**Outcome**	**Result**
IRT assumptions and model fit		
Exploratory Factor Analysis of one-factor model	Eigenvalue first factor	30.1
	Eigenvalue second factor	2.8
	Ratio	10.7
Confirmatory Factor Analysis of one-factor model	Scaled CFI	0.93
	Scaled TLI	0.93
	Scaled RMSEA	0.10
	Scaled SRMR	0.09
Local Dependency, one-factor model	Residual correlation > 0.20	34 item pairs locally dependent (3.3%)
Local Dependency of bi-factor model	Residual correlation > 0.20	3 item pairs locally dependent (0.4%)
Exploratory bi-factor analysis	ECV	0.68
	Omega-H	0.80
Monotonicity	Scalability coefficient H	0.63
	Scalability coefficients H_i	Range 0.55 – 0.70

CFI=Comparative Fit Index, ECV=Explained Common Variance, RMSEA=Root Means Square Error of Approximation, SRMR=Standardized Root Mean Residual, TLI=Tucker-Lewis Index

Measurement invariance

No DIF was found for age, one item was flagged for DIF regarding gender, 7 items were flagged for DIF regarding center, three items were flagged for DIF regarding duration of complaints, and 15 items were flagged for DIF regarding location of complaints (Table 4). The impact of all DIFs on total scores was negligible (Appendix 1 shows the differences between the initial theta and theta corrected for DIF for location of complaints; 75% of these differences were roughly between -0.075 and 0.06 theta points). When analyzing DIF for language, one item was flagged for non-uniform DIF and three items were flagged for uniform DIF (Table 4). The impact of DIF for language on the total score was negligible providing evidence for cross-cultural validity (Table 4).

Precision

The three items with the highest information at $\theta = 0$ (average of this Dutch sample) were PFB30 (*"Are you able to open a new milk carton?"*), PFA28 (*"Are you able to open a can with a hand can opener?"*) and PFA18 *("Are you able to use a hammer to pound a nail?")*. Figure 1 shows the standard errors across T-scores for the full item bank, the standard 7-item short form and the two simulated CATs as well as the distribution of scores in the patient population based on the US item parameters. A theta could reliably be estimated (>0.90) for 498/521 (95.6%) of the patients based on the full item bank and for all patients in the clinical range (T-score<50). A theta could reliably be estimated for 460/521 (88.3%) of the patients based on the 7-item short form, and for all but five patients with T-scores lower than 45. Using the standard CAT, a reliability of >0.90 was obtained for 469/515 (91.1%) of the patients and for all except three patients with a T-score<50. The average number of items administered was 4.7 and 83.3% of the patients needed less than 7 items to get a reliable score. For the fixed 7-item CAT, a reliability of >0.90 was obtained for 450/515 (87.4%) of the patients and for all patients with a T-score<47.

Comparative precision. The DASH showed some lack of unidimensionality (CFI 0.91, TLI 0.90, RMSEA 0.13, SRMR 0.08) but all items fitted a GRM model. The QuickDASH showed adequate unidimensionality (CFI 0.94, TLI 0.92, RMSEA 0.15, SRMR 0.08) and all items fitted a GRM model. The MHQ-ADL showed an even better unidimensionality (CFI 0.99, TLI 0.99, RMSEA 0.13, SRMR 0.03) and all items fitted the GRM model. Figure 2 shows the reliability of the Dutch-Flemish DF-PROMIS-UE v2.0 short form and standard CAT versus the DASH, QuickDASH and MHQ-ADL. The 30-item DASH displayed better reliability than the DF-PROMIS-UE 7-item short form and standard CAT (Figure 2a). The 11-item QuickDASH showed comparable reliability to the DF-PROMIS-UE CAT and short form (figure 2b). The 7-item MHQ-ADL displayed better reliability than the DF-PROMIS-UE 7-item short form and standard CAT for T-scores between T-scores of about 28 to 50, but for patients with low function the DF-PROMIS-UE v2.0 7-item short form and standard CAT performed better (Figure 2c).

Table 4. Result with respect to the monotonicity assumption and GRM-model fit at the item level, GRM-model item parameters, and measurement invariance of the DF- IS-UE v2.0 bank

Item		Monotonicity	GRM-model fit
ID	**Item phrasing**	**Scalability coefficient H_i**	**S-X^2 *p*-value**
PFA14r1	Are you able to carry a heavy object (over 10 pounds/5 kg)?	0.591	0.181
PFA16r1	Are you able to dress yourself, including tying shoelaces and buttoning your clothes?	0.639	0.021
PFA17	Are you able to reach into a high cupboard?	0.550	0.677
PFA18	Are you able to use a hammer to pound a nail?	0.656	0.451
PFA20	Are you able to cut your food using eating utensils?	0.642	0.003
PFA28	Are you able to open a can with a hand can opener?	0.679	0.063
PFA29r1	Are you able to pull heavy objects (10 pounds/5kg) towards yourself?	0.629	0.363
PFA34	Are you able to wash your back?	0.604	0.353
PFA35	Are you able to open and close a zipper?	0.606	0.247
PFA36	Are you able to put on and take off a coat or jacket?	0.579	0.408
PFA38	Are you able to dry your back with a towel?	0.622	0.596
PFA40	Are you able to turn a key in a lock?	0.611	0.729
PFA43r1	Are you able to write with a pen or pencil?	0.592	0.242
PFA44	Are you able to put on a shirt or blouse?	0.606	-.482
PFA48	Are you able to peel fruit?	0.634	0.149
PFA50	Are you able to brush your teeth?	0.612	0.211
PFA54	Are you able to button your shirt?	0.630	0.140
PFB11	Are you able to wash dishes, pots, and utensils by hand while standing at a sink?	0.638	0.251
PFB13	Are you able to carry a shopping bag or briefcase?	0.593	0.010
PFB15r1	Are you able to change the bulb in a table lamp?	0.641	0.768
PFB16r1	Are you able to press with your index finger (for example ringing a doorbell)?	0.596	0.071
PFB18	Are you able to shave your face or apply makeup?	0.645	0.377
PFB19r1	Are you able to squeeze a new tube of toothpaste?	0.663	0.518
PFB20r1	Are you able to cut a piece of paper with scissors?	0.651	0.071
PFB21r1	Are you able to pick up coins from a table top?	0.603	0.013
PFB22	Are you able to hold a plate full of food?	0.662	0.489
PFB23r1	Are you able to poor liquid from a bottle into a glass?	0.661	0.002
PFB25	Are you able to push open a door after turning the knob?	0.593	0.257

GRM-model Item parameters					Measurement invariance									
a	b1	b2	b3	b4	Gender		Center		Duration of complaints		Location of complaints		Language	
					UF	R^2	UF	R^2	UF	R^2	UF	R^2	UF	R^2
1.862	-0.613	-0.227	0.415	1.054										
2.780	-1.757	-1.097	-0.397	0.444										
1.670	-1.156	-0.587	-0.046	0.657							UD	0.118		
3.027	-0.768	-0.421	-0.059	0.361										
3.028	-1.553	-0.985	-0.376	0.172			UD	0.032						
3.404	-0.738	-0.431	-0.111	0.463			UD	0.027						
2.266	-1.068	-0.534	-0.066	0.771										
1.989	-0.906	-0.343	0.249	1.077							UD	0.028		
2.572	-2.203	-1.347	-0.704	0.099										
1.968	-2.736	-1.438	-0.495	0.604							UD	0.043		
2.378	-1.488	-0.923	-0.181	0.682							UD	0.028		
2.545	-1.992	-1.446	-0.922	-0.342										
2.345	-1.857	-1.371	-0.843	-0.401										
2.222	-2.361	-1.439	-0.624	0.473										
2.983	-1.187	-0.877	-0.491	0.058			UD	0.050			UD	0.027		
2.310	-2.416	-2.001	-1.292	-0.614										
2.783	-1.871	-1.330	-0.730	0.084			UD	0.023	UD	0.020	UD	0.023		
2.928	-1.421	-0.825	-0.375	0.303										
1.926	-1.262	-0.808	-0.126	0.580							UD	0.027		
3.067	-1.280	-1.012	-0.571	-0.001										
2.165	-2.651	-2.110	-1.510	-0.950									UD	0.025
3.073	-1.810	-1.411	-0.841	-0.101										
3.177	-2.142	-1.667	-1.055	-0.410										
3.313	-1.624	-1.229	-0.844	-0.310							UD	0.021		
2.164	-2.350	-1.916	-1.389	-0.677									UD	0.043
2.965	-1.488	-1.153	-0.639	0.103										
3.046	-1.692	-1.373	-0.798	-0.151										
2.157	-2.353	-1.524	-0.966	-0.182										

Table 4. Continued

Item		Monotonicity	GRM-model fit
ID	**Item phrasing**	**Scalability coefficient H_i**	**S-X^2 *p*-value**
PFB26	Are you able to shampoo your hair?	0.644	0.331
PFB27	Are you able to tie a knot or a bow?	0.640	0.015
PFB28r1	Are you able to lift 10 pounds (5 kg) above your shoulder?	0.639	0.081
PFB30	Are you able to open a new milk carton?	0.675	0.035
PFB31r1	Are you able to open car doors?	0.654	0.181
PFB33	Are you able to remove something from your back pocket?	0.577	0.478
PFB34	Are you able to change a light bulb overhead?	0.638	0.311
PFB36	Are you able to put on a pullover sweater?	0.595	0.475
PFB37r1	Are you able to reach and get down a 5 pound (2 kg) object from above your head?	0.660	0.724
PFB39r1	Are you able to reach and get down a 5 pound (2 kg) object from above your head?	0.626	0.605
PFB41	Are you able to trim your fingernails?	0.586	0.595
PFB56r1	Are you able to lift one pound (0.5 kg) to shoulder level without bending your elbow?	0.563	0.250
PFC43	Are you able to use your hands, suchs as for turning faucets, using kitchen gadgets, or sewing?	0.619	0.045
PFC49	Are you able to water a house plant?	0.662	0.016
PFM2	Are you able to lift a heavy painting or picture to hang on your wall above eye-level?	0.684	0.720
PFM16	Are you able to pass a 20-pound (10 kg) turkey or ham to other people at the table?	0.697	0.275
PFM18	Are you able to continuously swing a baseball bat or tennis racket back and forth for 5 minutes?	0.624	0.131
PFC8	Does your health now limit you in opening a previously opened jar?	0.617	0.203

ID=Identification, GRM=Graded Response Model, NUD=Non-Uniform DIF, ID=UD=Uniform DIF, UF=Uniformity

GRM-model Item parameters					Measurement invariance									
a	b1	b2	b3	b4	Gender		Center		Duration of complaints		Location of complaints		Language	
					UF	R^2	UF	R^2	UF	R^2	UF	R^2	UF	R^2
2.907	-1.470	-1.009	-0.496	0.287										
3.027	-1.429	-0.959	-0.570	0.042			UD	0.056	UD	0.031				
2.040	-0.198	0.224	0.670	1.350							UD	0.062		
3.590	-1.449	-0.990	-0.520	0.100										
2.906	-1.773	-1.330	-0.798	-0.181										
2.045	-1.626	-1.104	-0.576	0.209										
2.357	-0.717	-0.357	0.079	0.824							UD	0.052		
2.061	-2.009	-1.148	-0.265	0.618							UD	0.058		
3.125	-1.980	-1.547	-0.978	0.348										
2.218	-0.886	-0.533	-0.055	0.705					UD	0.022	UD	0.030		
2.352	-1.487	-1.091	-0.547	0.001			UD	0.038						
1.816	-1.004	-0.604	-0.191	0.508							UD	0.041		
2.853	-1.755	-1.243	-0.713	-0.069			UD	0.232			UD	0.024		
3.091	-1.807	-1.431	-1.056	-0.463	UD	0.028							UD	0.022
2.786	-0.431	-0.083	0.377	1.208									NUD	0.021
2.698	-0.212	0.176	0.677	1.469										
1.941	-0.339	0.091	0.553	1.239							UD	0.028		
2.460	-1.903	0.999	-0.365	0.391										

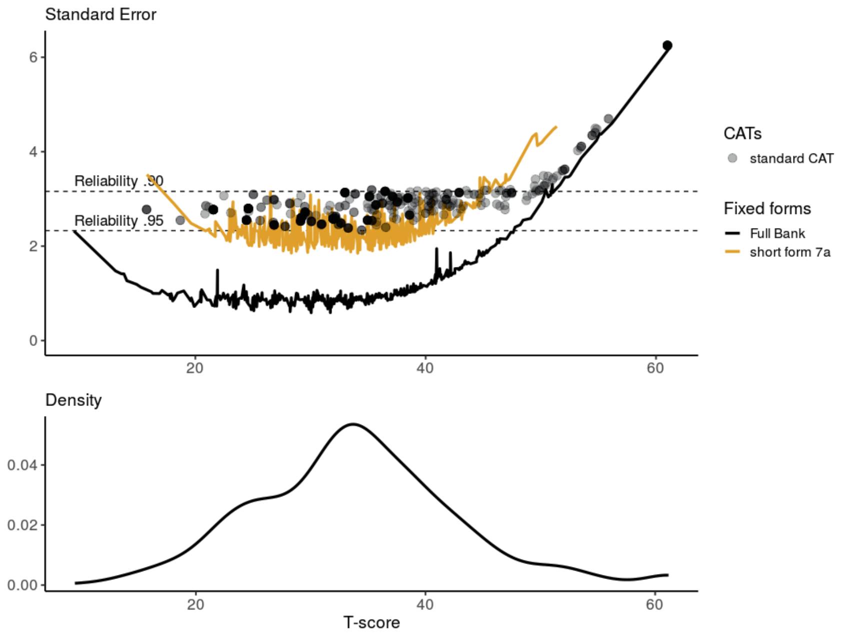


Figure 1. Reliability of the DF-PROMIS-UE v2.0 when using different applications (full item bank, 7-item short form and simulated standard CAT. Shading represents many of the same scores. The density plot represents the distribution of T-scores in the study sample.

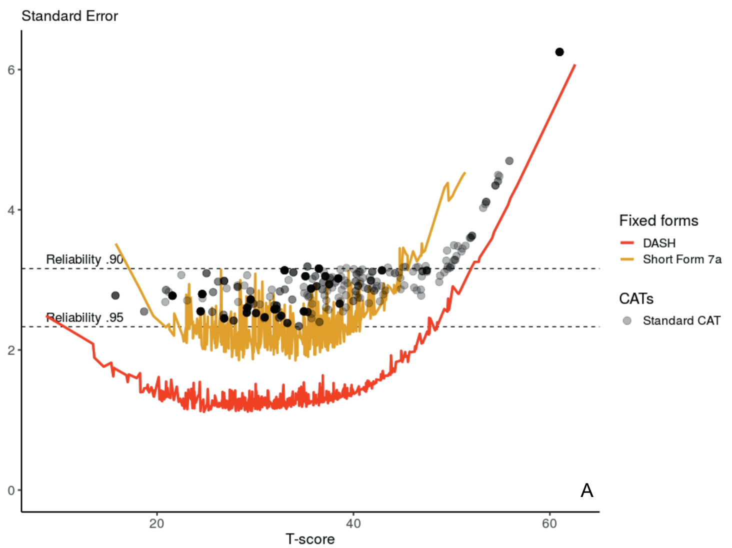


Figure 2a. Reliability of the CAT of the DF-PROMIS-UE v2.0, the 7-item short form and the DASH.

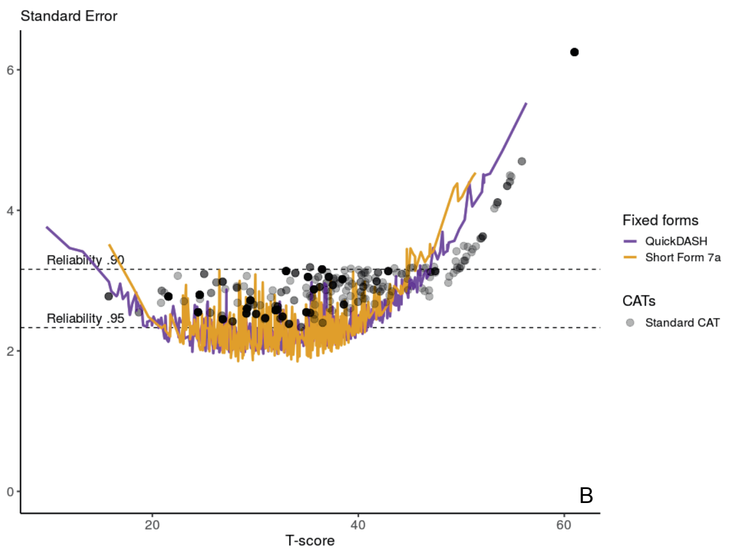


Figure 2b. Reliability of the CAT of the DF-PROMIS-UE v2.0, the 7-item short form and the QuickDASH

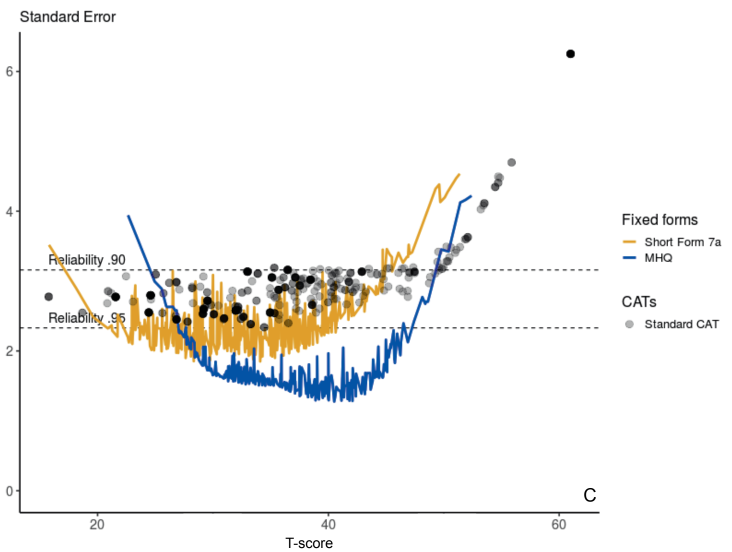


Figure 2c. Reliability of the CAT of the DF-PROMIS-UE v2.0, the 7-item short form and the MHQ-ADL

Relative efficiency. The DF-PROMIS-UE 7-item short form is on average more efficient than the full item bank. The DF-PROMIS-UE CAT is on average more efficient than the DF-PROMIS-UE full bank and 7-item short form and more efficient than the DASH, QuickDASH and MHQ (Table 5). The DF-PROMIS-UE 7-item short form and full item bank are on average more efficient than the DASH and QuickDASH, but less efficient than the MHQ (Table 5).

Table 5. Mean relative efficiency of PROMIS measures versus legacy instruments

	DF-PROMIS-UE full bank (46 items)	DF-PROMIS-UE 7-item short form (7 items)	DF-PROMIS-UE standard CAT (average 4.7 items)
DF-PROMIS-UE full bank (46 items)		1.37	1.54
DF-PROMIS-UE 7-item short form (7 items)			1.30
DASH (30 items)	1.30	1.50	1.82
QuickDASH (11 items)	1.42	1.58	1.96
MHQ (7 items)	0.79	0.95	1.12

DASH=Disability of Arm, Shoulder and Hand, DF-PROMIS-UE v2.0= Dutch-Flemish translated version of the PROMIS Upper Extremity v2.0 item bank, MHQ-ADL=Michigan Hand Questionnaire-Activities of Daily Living subscale

DISCUSSION

We validated the DF-PROMIS-UE v2.0 item bank in a Dutch population with upper extremity disorders. This study comprises the first foreign language validation of this item bank. We found sufficient evidence for the assumptions of the IRT model, good IRT model fit and a high reliability across a wide range of the construct for the DF-PROMIS-UE v2.0 item bank. We found no evidence for DIF due to age, but some items were flagged for DIF for gender, center, duration of complaints, location of complaints, and language. However, the impact of DIF on T-scores was considered negligible.

With regard to unidimensionality, CFI and TLI values (0.93 and 0.93) were near the minimum criteria of 0.95, RMSEA was higher than the maximum criterion of 0.06 (0.10) and SRMR was slightly higher than the maximum criterion of 0.08 (0.09). A few studies reported on the validation of the PROMIS-UE v1.2 item bank, but none described the CFI, TLI, RMSEA, or SRMR values [41,43-46]. A high RMSEA has been reported for many other PROMIS item banks [47-50]. It has been suggested that traditional cutoffs and standards for CFA fit statistics, are not suitable to establish unidimensionality of item banks measuring health concepts and bi-factor analysis has been suggested to examine whether a scale is 'unidimensional enough' [51]. The bi-factor analysis results suggest sufficient unidimensionality of the DF-PROMIS-UE v2.0 item bank.

We studied DIF for age, gender, center, duration of complaints, location of complaints, and language, as the scores of groups differing with respect to these variable, are frequently compared in studies. Our study results indicate that is legitimate to compare these groups when applying the DF-PROMIS-UE v2.0 measure. However, the DIF results all seem to be related to a difference in performance between items regarding fine tactile function versus items regarding lifting heavy objects. For example, all DIF results for location of complaint indicated that among patients with the same overall level of UE functioning, patients with only hand/wrist injuries indicated more problems with activities that involve fine tactile functioning and patients with only shoulder problems indicated more problems with activities involving heavy lifting tasks, reaching above shoulder level or behind the back. It is known that grip strength is merely a reflection of overall muscle strength and condition of a chain of muscles in the upper limb and at long term follow-up is not severely impacted by hand or wrist injury [52-54]. In contrast, range of motion is significantly impacted by hand and wrist injuries and influences fine tactile functioning [53-55]. Therefore, we hypothesize that arm/shoulder problems impact heavy lifting activity, but to a lesser extent fine tactile functioning. Even though in our study the impact of DIF for location of complaints on total scores seemed negligible (Appendix 1), more research in other populations with different distribution of injuries of the upper extremity should be performed to investigate the impact of DIF for location of complaint.

When studying measurement invariance for language (cross-cultural validity), we found 3 items with DIF. None of these DIF items are included in the standard 7a short form. Item PFM2 was selected as second item in the standard CAT in 15.9% of the patients, but the R^2 change is very small (0.0212) so the impact might be small. Crins *et al.* examined language DIF of the PROMIS Physical Function v1.2 in a study in chronic pain patients. They found four items with language DIF, of which one item (PFB13 '*Are you able to carry a shopping bag or briefcase?*') is also included in the PROMIS-UE v2.0 item bank. This item was not flagged for language DIF in our study. In contrast to our study, Crins *et al.* did not find DIF for any of the items flagged for DIF in our study that were also included in the PROMIS Physical Function v1.2 item bank [49]. It has been suggested that such differences can occur because most available DIF methods can detect whether there is DIF but cannot identify the exact DIF items due to parameter identification issues [56]. Our study and the study of Crins *et al.*, found minimal impact of language DIF on T-scores, which suggests that the original US item parameters can be used for calculating the T-scores of the DF-PROMIS-UE v2.0 bank.

We found high reliability of simulated standard CAT T-scores with a reliability of > 0.90 (which has been considered a minimum requirement for use of PROMs in individual patients [57]) in 91.7% of the patients and in all patients within the clinical range, with on average only 4.7 items. The short form 7a had a reliability of >0.90 in 88.5% of the patients. The short form was slightly more reliable than the standard CAT in the middle of the scale for T-scores between 18 and 45 but performed less than the CAT in patients with low function (range of T-score in the study population was 11-61). Both the standard CAT and the short form had sufficient reliability but the CAT required less items. The DASH displayed better reliability than the DF-PROMIS-UE v2.0 standard CAT and 7-item short form, while the QuickDASH displayed comparable reliability. However, the DASH requires 30 items, which may be considered too much for use in daily clinical practice. The MHQ-ADL is less reliable than the DF-PROMIS-UE v2.0 measures in patients with low functioning. Future studies should examine whether it is possible to further improve the standard CAT by choosing another starting item. Currently, item PFM16 is being used ('*Are you able to pass a 20-pound (10 kg) turkey or ham to other people at the table?*'), but this item is less informative (ranked 14) in the Dutch sample and was flagged for language DIF in the level 2 traumacenter [16].

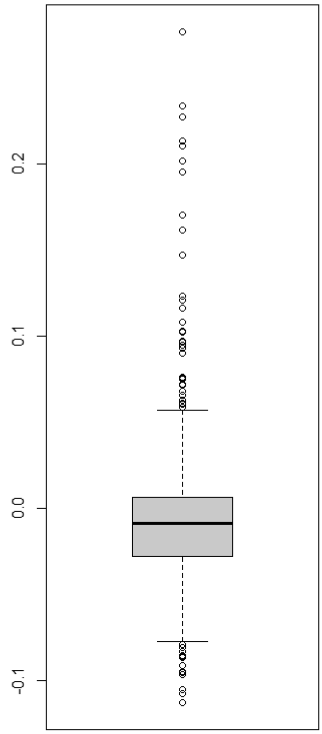
For adequate interpretation, a PROM has to be validated in the language in which it will be used, as we have done for the DF-PROMIS-UE v2.0. Van Eck *et al.* have performed validation of the DASH-Dutch Language Version and showed that it also measures a unidimensional trait [20]. Iordens *et al.* performed validation of the Dutch translated version of the QuickDASH [58]. Unfortunately, to our knowledge, the MHQ has not been validated in the Dutch language. This might hamper the interpretability of the outcome presented in this study with respect to the MHQ. On the other hand, our own study provides evidence for the adequate unidimensionality and reliability of the MHQ-ADL.

When reporting on outcomes of UE disorders in literature, extensive core sets including functional outcomes and PROMs have been suggested to improve comparability of studies [59,60]. However, for clinical practice, a more practical 'lean' core set is advisable including a PROM with low burden for the patient and clinician. An advantage of the incorporating the DF-PROMIS-UE v2.0 in this 'lean' core set is that it has high correlation with other PROMs reporting on UE disorders, it decreases burden for patients and clinicians and it will allow clinicians to speak a 'common language' with regards to outcome reporting [17,61]. However, the PROM should be able to detect clinical relevant change as expressed in the minimal important change (MIC). De Vet *et al.* defined MIC as 'the smallest change in construct to be measured which patients perceive as important' [62]. The MIC threshold is very important in daily practice, where clinicians can compare at a patients' individual level the current and previous values of outcome measures of interest. The MIC has been estimated for the DASH, QuickDASH, and MHQ [58,63,64]. However, for the PROMIS-UE v2.0 a MIC has not been established. Future research regarding test-retest reliability, smallest detectable change, and MICs is mandatory to be able to interpret outcome as reported with the DF-PROMIS-UE v2.0 in clinical practice.

Conclusions

The DF-PROMIS-UE v2.0 item bank showed sufficient psychometric properties in a Dutch population with injuries of the upper extremity. This item bank is now ready for use as CAT in research and clinical practice and will be made available through the Dutch-Flemish Assessment Center (http://www.dutchflemishpromis.nl). However, test-retest reliability, responsiveness, and MICs need to be assessed in future studies. DF-PROMIS-UE v2.0 CATs allow reliable and valid measurement of outcome following musculoskeletal disorders of the upper extremity in an efficient and user-friendly way with limited administration time.

Appendix 1. Differences between the initial theta and theta corrected for DIF for location of complaints.



The box shows the interquartile range, representing the middle 50% of the differences.

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CHAPTER 9

General discussion, future perspectives and conclusions

GENERAL DISCUSSION, FUTURE PERSPECTIVES AND CONCLUSIONS

General objective

The *general objective* of this thesis was to gain insight in radiological measurements, clinician reported outcomes (CROs) and patient reported outcomes (PROs) following hand and wrist injuries in non-osteoporotic patients. We have aimed to report on the prevalence of posttraumatic arthritis (PA) in these young non-osteoporotic patients and to describe the association between radiological measures, CROs and PROs following distal radius fractures (DRFs). Our second objective was to report on CROs and PROs following perilunate (fracture) dislocations (PLD/PLFDs). In addition, we intended to validate several PROs in the Dutch translation for upper extremity injuries. Finally, the purpose of this thesis was to put outcomes in perspective by reporting on their clinical relevance.

Posttraumatic arthritis following distal radius fractures

Prevalence

From the systematic review and our studied cohort of non-osteoporotic patients presented in this thesis, we conclude that the prevalence of PA following a distal radius fracture (DRF) was high at medium to longterm follow-up (respectively 37%-50% with follow-up ranging 18 months-38 years and 32% with median follow-up 62 months). In our cohort, all patients with PA had grade I or II after a follow-up of 5 years [1]. Based on our results we suggest that PA is a progressive process and changes significantly over time (prevalence of PA 31% at ≤36 months and 64% with >36 months follow up, respectively) [2]. This is supported by Forward *et al.* who described a cohort of young patients following DRFs at a mean follow-up of 38 years [3]. Although they reported a comparable prevalence of PA, after this long follow-up duration the grading of PA was worse (all grade II or III). We state that it is of importance for the young patient to comprehend that PA develops and progresses over time following DRFs, in the light of an expected long active working life.

PA and the association with age

Basic scientific and clinical studies have shown that older age is an important risk factor for the development of PA due to age-related changes in articular chondrocytes which results in altered ability to respond to cartilage damage [4-6]. We have chosen to select a young group of patients to investigate the influence of hand and wrist injury, who have a long active life ahead of them, because we reckon they have higher functional demands than older patients. A reason of not finding an association between age and PA in our study, could be that we selected young patients with normal functioning articular chondrocytes. In contrast, other authors reporting on DRFs in patients with wider age ranges did show an association between older age and higher prevalences of PA up to 65% of PA after 6.7 years [1,3].

<u>*Radiological measurements*</u>

Articular incongruency. In the presence of articular surface incongruency and joint instability there is an abnormal loading of the cartilage and subchondral bone, which leads to progressive cartilage degeneration [7,8]. This can decrease the cartilage repair potential, forming an ongoing vicious cycle and resulting in progression of PA over time [4]. To avoid this vicious cycle, it has been advocated to treat intraarticular fractures with anatomical reduction and stable fixation of articular fragments, which consequently results in reduction of the cartilage surface [9]. The studies included in our systematic review reported that DRFs healed with a step-off > 2mm are associated with development of PA [1,10-15]. However, in our cohort study no statistically significant association between articular incongruency and PA was present. This may be explained by the fact that, although 56 patients had some articular incongruency, only in 7 patients this exceeded 2 mm at follow-up. In addition, the grading of PA might not be severe enough yet to prove an association with articular incongruency due to a relatively short follow-up period. With longer follow-up duration, other authors have described an association between articular incongruency and PA [3]. We therefore conclude that intraarticular incongruency should be diminished with adequate reduction and stable fixation, where applicable, should be pursued to avoid PA in this young non-osteoporotic patient cohort.

Ligamentous injury. DRFs in young patients most often result from high-energy trauma and therefore most often are intraarticular fractures, which are associated with concommitant ligamentous injuries [16-20]. Prevalences up to 98% of associated ligamentous injury with DRFs, mostly scapholunate (SL) ligament injuries, have been described [21,22]. Similar to the genesis of ligamentous injury in distal DRFs, in carpal injuries, SL ligament injury is the first stage in the injury cascade that takes place in perilunate (fracture) dislocations (PLD/PLFDs) and can result in joint instability (according to the mechanism as described by Mayfield (Chapter 1, Figure 2) [23,24]. Progress over time of this joint instability is known as scapholunate advanced collaps (SLAC) and is known to result in radiocarpal PA [20]. Unfortunately, SL injuries are difficult to diagnose on plain radiographs, as only Geissler type IV lesions are represented by a distance between scaphoid and lunate > 2mm due to a complete tear [20,21,25]. In our study population, 30 patients had SL-distances exceeding 2mm, but no association with PA was present. Mrkonjic *et al.* support our finding that associated scapholunate injury in patients following DRF does not have to result in PA by scapholunate advanced collapse after long-term follow-up [26]. They reported no SLAC and subsequent PA at 15 years following DRFs with arthroscopically proven SL injuries. They hypothesized that radiographic instability of the SL ligament is not necessarily presented with clinical instability as tested with the Watson shift test [27]. Clinical instability is dependent on which anatomical portion of the SL is injured; it is known that the dorsal portion is most important for stability as well as extrinsic dorsal stabilizators [28]. Partial rupture of the SL ligament (for instance the volar portion) does not necessarily result in clinical instability. In addition, possibly the healing potential of the SL ligament might add to regaining a clinical stable situation following DRFs [26].

Other radiological measurements. With regard to other radiological measurements as predictors for PA, literature reported conflicting results [3,11,29,30]. In our study, the only radiological measurement that was associated with PA was radial length. Patients with PA had a statistically significant longer radial length (1mm) in comparison to patients without PA. In addition, in the patients with PA, the radial length of the injured wrist was also significantly longer (1.2mm) in comparison to the uninjured wrist. However, these measurements fall within error magnitude as reported by Watson *et al.* and therefore might be explained by measurement error [31].

To our knowledge, no studies reported on longer radial length and the association with PA. In contrast, Forward *et al.* reported on radial shortening of 2mm resulting in a 2.4 times higher risk on PA than with no shortening in radial length with a mean follow-up duration of 38 years [3]. However, most studies included in the systematic review reported no significant association with shortened radial length and the development of PA [1,32,33]. The development of PA has multifactorial causes, such as increased stress on the articular surface that damages cells and matrices of articular cartilage and subchondral bone [4]. So adequate correction of the radial length radius following DRFs seems to be important to decrease the risk on PA. However, further research regarding the influence of radial length on the development of PA is mandatory.

PA and CROs

aROM. The included studies in the systematic review reported conflicting results regarding the association between PA and active range of motion (aROM); four studies described a significantly diminished flexion or flexion/extension [2,13-15]. One study described poor supination [12] and five studies reported no statistically significant association between PA and aROM (Chapter 2) [34-38]. All included studies described small populations, which might be an explanation for the conflicting outcomes. To overcome this, pooled data analysis of the open source data of seven studies was performed, revealing that only the aROM measurement radial deviation was statistically significantly worse in patients with PA in comparison to patients without PA (mean difference 3°) [12,13,15,35,37,39,40]. This mean difference is however within error magnitude and might be explained by measurement error [31]. When analyzing our patient cohort (Chapter 3), patients with PA had clinically relevant (and statistically significant) diminished flexion/extension (12°) and ulnar/radial deviation (6.3°) [41]. Although our cohort was comparable to the cohorts in the studies included in the systematic review regarding age and fracture type, the included number of patients in the studies reporting on an association between PA and aROM were mostly smaller than ours. In addition, the length of follow-up differed extensively between the studies. These factors might be the reason for the different results reported in our study (Chapter 3) in comparison with the results reported in the studies included in the systematic review (Chapter 2). With the expected progression of PA and a long active life ahead in these young patients, the knowledge that diminished flexion/extension and ulnar/radial deviation can be expected following DRFs is of importance to these young patients and their treating clinicians.

Grip strength. PA was not associated with diminished grip strength measurements in young patients following DRFs. Grip strength does not seem to be a determinant of hand or wrist function alone, but merely a reflection of overall muscle strength of the entire upper limb [42].

PA and PROs

Little is written in literature on the association between PA following DRFs and PROs. In the cohort study presented in Chapter 3, patients with PA had significantly lower scores on the MHQ subscales 'general functioning, 'esthetics', 'satisfaction' and total MHQ score. In addition, the SF-36 subscale 'physical functioning' was statistically significantly lower in patients with PA. The question arises if these differences withold clinical relevant changes. Unfortunately, to our knowledge, no Minimal Important Changes (MICs) have been reported for these PROs. For DASH and PRWE subscales and total scores reference MICs are available [43,44] and only the difference between patients with PA and without PA on PRWE subscale 'pain' exceeded the reported MIC. However, the validated Dutch language version of the PRWE (PRWE-NL) seems to measure a unidimensional trait, so reporting on the subscale 'pain' in the Dutch translated version is not advocated [45]. Therefore, reporting MICs for the PRWE subscales might not be advisable. Our results suggest that PA does not have a clinical relevant impact as perceived by patients based on results gathered from the DASH and PRWE. Another possibility is that these questionnaires might not be the right tools to differentiate between patients with limitations due to PA or without. As a consequence, in our opinion both questionnaires cannot be used to monitor progression of PA in patients who sustained a DRF. The statistically significant associations between PA and the MHQ and SF-36 suggest that PA does impact non-osteoporotic patients following DRFs. The MHQ seems a promising tool to differentiate between patients who do or do not experience limitations due to PA following hand and wrist injury. To gain better insight into the clinical relevance of PA, MICs regarding the MHQ and SF-36 should be obtained.

Radiological measurements

Evolution

Patients following DRFs did not show signs of changes in radiological measurements in the first 6 weeks post-injury (Chapter 4), which is remarkable. Neidenbach *et al.* stated that changes did occur in these first 6 weeks following DRFs [46]. One of the possible explanations for their finding was that in their study, unstable DRFs were treated with conservative management, resulting in early dislocation. In our study, DRFs with unstable characteristics were treated with open reduction and stable fixation according to the Dutch guidelines for treating DRFs [47,48]. The earlier mentioned study reported no radiological changes between 6 weeks and 1 year follow up [46]. In contrast, our study did suggest that ulnar variance and radial inclination increased and step-off and gaps diminished statistically significantly during 5 years following DRFs. However, all these changes were minimal (≤ 1mm or ≤ 1°) and did not exceed reported error magnitudes suggesting they might be classified as measurement error [31].

If ulnar variance and radial inclination increase, but radial length does not increase, a compression (and relative shortening) of the ulnar side of the distal radius must be present. Rikli and Regazzoni described this anatomical area in 1996 as the intermediate column [49,50]. It consists of the lunate facet and the sigmoid notch and is responsible for >50% of the axial compressive forces that are transmitted across the wrist during normal activity [51]. Brink and Rikli acknowledged the importance of the intermediate column and described the volar and dorsal 'key corner' of the intermediate column. They stated that control with reduction and stable fixation of this 'key corner' should be the first step of the surgical strategy after a DRF, because insufficient treatment may result in joint instability and carpal subluxation [50]. The changes over time as presented in our study might be the result of some instability of this 'key' corner, although changes were minimal.

As stated earlier, step-offs and gaps seemed to diminish over time in our study. Residual step-offs and gaps with concominant cartilage injury have been related to insufficient remodelling processes of subchondral bone leading to the development of PA [52]. In contrast, animal studies have suggested that the extent of incongruency following intraarticular fractures might diminish due to cartilage and subchondral bone remodelling responses [53]. To our knowledge, no literature on a decrease in articular incongruency in adult patients is available. Bone healing is a complex event that involves coordination of two complex forces: anabolism or tissue formation and catabolism or remodelling under influence of axial, translational and rotational forces [54,55]. Possibly a form of remodelling diminishes the articular incongruence, but further research is mandatory.

Reference values

Mean radiological measurements at follow-up of the reported DRFs in this thesis were within reported normal ranges, although several patients did have radiological measurements exceeding reference values. Normal reference values regarding radiological measurements following DRFs have been reported in literature (Chapter 1, Figure 3) [56-64]. Some studies reported on small populations and were published between 1976 and 2018 with most likely varying quality of radiographic imaging over time. To overcome the shortcomings of comparing radiological measurements with reported reference values, we have used the measurements of the uninjured wrist as a reference to ensure correction for anatomical variation between patients. Of all radiological measurements, only a statistical significantly more pronounced dorsal angulation was present in the injured wrist compared to the uninjured wrist (Chapter 4). This measurement change did not exceed reported error magnitude [31] and thus might be explained by measurement error. Our results may suggest that adequate treatment has been provided to the patients, but may also suggest that the reported reference measurements have such wide ranges that patients in our study only exceeded reference values minimally. More importantly, the question arises what the clinical implications of radiological measurements are. Acceptable alignment has not been defined yet in terms of clinical relevance. The reported reference values for radiological measurements following DRFs might not reflect the thresholds for a clinical relevant impact on outcomes. We suggest the use of radiological measurements of the uninjured wrist as reference. We advise to determine minimal important changes (MICs) regarding radiological measurements to put reference values in perspective in terms of clinical relevance.

Radiological measurements, CROs and PROs

The associations between PA, residual articular incongruency and worse outcome regarding aROM and PROs seem to be complex. Regarding radiological measurements, only step-off was associated with diminished flexion/extension, radial/ulnar deviation and worse SF-36 'mental component' score with statistical significance (Chapter 4). In addition, we have shown that articular incongruency was associated with PA. Also, PA was associated with worse aROM measurements and PROs (Chapter 2-3). In addition, diminished aROM measurements were associated with diminished PROs (Chapter 3). Because our population was relatively small, we have chosen not to compare patients who can be categorized within or out of radiological reference values as reported in literature. A recent systematic review regarding the association between radiological measurements and PROs following DRFs has hypothesized that radiological measurements exceeding reported reference values (Chapter 1, Figure 3) are less well tolerated by young active patients in comparison to patients older than 60-65 years of age [65]. The two included studies that stratified for age showed a clinically relevant difference between acceptable and unacceptable alignment regarding the PRWE and DASH scores for patients younger than 60-65 years and not in older patients [66,67]. Besides step-off, the radiological measurements in our study might not have been pathological 'enough' to show associations with PROs.

Clinician reported outcomes

Active range of motion

Flexion/extension and radial/ulnar deviation seem to be cinically relevantly diminished following DRFs and PLD/PLFDs in our groups of young non-osteoporotic patients when comparing these CROs to healthy controls, but also when comparing outcomes to the uninjured wrist (Table 1 & Chapter 3-5) [41]. Although not statistically tested, PLD/PLFD patients seem to have worse aROM measurements than patients following DRFs (Table 1). This may imply that a PLD/PLFD is a more severe injury with poor functioning in comparison to a DRF. For DRF patients, diminished aROM was associated with PA and articular incongruency (Chapter 3-4). For the patients following PLD/PLFDs we could not calculate such associations due to the limited sample size (Chapter 5). However, it is known that PLD/PLFDs may lead to PA due to joint instability resulting in SLAC [68-70]. This could be an explanation for the diminished aROM measurements in these patients. Karagiannopoulos *et al.* are the only authors reporting on MIC regarding aROM following DRFs using an anchor-based method (N= 33, mean age 59.7 years, follow-up 8-12 weeks) [41]. No MICs were reported for ulnar/radial deviation or pro/supination. The target population was comparable to our population, although the reported population was older than non-osteoporotic age ranges and the sample size was small. We hypothesize that younger patients may have even lower thresholds for noticing a decrease in aROM in every day life, because of their high demand of hand and wrist function. MICs for all aROM measurements need to be calculated in a younger population following DRFs and PLD/PLFDs, to determine actual clinical relevance of diminished function of hand and wrist for this cohort. When councelling patients regarding their hand or wrist injury and the expected outcome, it should be pointed out that diminished aROM can be expected.

Grip strength

Following DRFs no clinical relevant change in grip strength measurements was observed when comparing outcomes to the grip strength measurements of the uninjured wrist (Table 1 & Chapter 3). However, within the PLD/PLFD patients clinically relevantly diminished grip strength was present when comparing outcome with measurements of the uninjured wrist. This result remained present when excluding the patients receiving a wrist arthrodesis (Chapter 4). Again, this accentuates that a PLD/PLFD seems to be an injury with more severe consequences than a DRF. For DRFs, only grip strength was statistically significantly associated with shorter radial length (Chapter 4). Several reports have mentioned an association between radial shortening and diminished grip strength measurements [1,71-74]. Radial shortening can cause an increased pressure in the distal radio-ulnar joint (DRUJ) and a shift in the centre of pressure within the sigmoid notch and impact grip strength in a negative manner [75-77]. We hypothesize that radial length as measured in our study was not pathological enough to show statistically significantly diminished outcomes. In addition, it has been reported that grip strength is not a determinant of hand or wrist function alone, but merely a reflection of overall muscle strength of the chain of muscles of the upper limb [42]. In this light, our results regarding the PLD/PLFD patients are remarkable. We hypothesize that the limitations following PLD/PLFDs results in disuse and subsequently diminished overall muscle strength of the injured arm. Kim *et al.* presented the only research on MICs regarding grip strength measurements in 50 patients treated for a DRF with volar locking plate fixation using an anchor-based method at 1 year follow up [78]. Although the target population was comparable to our population, the sample size was small and ages were not reported. MIC values for grip strength measurements, such as power grip, sustained grip and key pinch grip, need to be calculated in larger patient populations with specific stratification for age, gender and injury characteristics to enable better interpretation of CROs. This can determine actual clinical relevance of grip strength for this cohort.

Table 1. Comparison of CROs of the studies of this thesis

CROs	DRF patients (N=73)	Uninjured wrist DRF patients	Mean difference DRF	PLD/PLFD patients (N=11)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Range of motion (°)				
Flexion/extension	141 (18)	153 (13)	-11.2 (12.6)*	90 (27)
Ulnar/radial deviation	58 (11)	65 (11)	-6.9 (9.9)	33 (14)
Supination/pronation	147 (13)	152 (11)	-5.3 (11.0)	155 (12)
Grip strength measurements (kg)				
Grip strength	43.5 (13.2)	46.1 (12.7)	-2.6 (6.0)	35.3 (16.0)
Sustained grip strength	24.6 (10.9)	25.0 (9.6)	-.4 (6.4)	22.3 (11.9)
Key pinch strength	8.5 (2.8)	8.7 (2.5)	-.1 (2.0)	8.5 (1.7)

N=number of patients, CROs=clinician reported outcomes, DRF=distal radius fracture, PLD/PLFD=perilunate (fracture) dislocation, MIC=minimal important change, °=degrees, kg=kilograms, *=difference exceeding MIC

Patient reported outcomes

From our studied cohort following DRFs, the PRWE was clinically relevantly diminished (Chapter 4). We concluded that some PROs are statistically significantly diminished in patients with PA and with residual articular incongruency (Chapter 3). In addition, substantial differences regarding PROs were encountered between patients with DRFs and PLD/PLFDs and exceeding MICs (Table 2). We may conclude that the latter patients seem to suffer more limitations, although we only investigated a limited sample size. PROs are becoming increasingly important to report on outcome following hand and wrist injuries. Several authors have adviced to report core sets of outcome measures (including CROs and PROs) to facilitate comparing outcomes reported in literature [80,81]. However, for clinical practice, these core sets seem too extensive and thus too time-consuming. Therefore, we advise a more practical version. The question arises which PRO to implement in this 'lean' core set?

It is important to understand what a PRO is actually measuring and if it is measuring the same construct as it was designed to do. It is known that by translating a PRO, the designed construct to be measured can change. Therefore, validation studies are necessary following translation. The original constructs of the DASH and the PRWE were designed to measure multiple subscores in the English language [82-84]. We concluded that the DASH-Dutch Language Version (DASH-DLV) measures a unidimensional trait in patients with upper extremity injuries and should be reported as a single score (Chapter 6). In addition, the Dutch version of the PRWE (PRWE-NL) has been validated by our research group and it was concluded that the PRWE-NL also measures a unidimensional trait in patients with upper extremity injuries [45]. Therefore, single scores

Uninjured wrist PLD/PLFD patients	Mean difference PLD/PLFD	Mean difference DRF – PLD/ PLFDs	Healthy controls (N=22)	MIC
Mean (SD)	Mean (SD)		Mean (SD)	
144 (16)	-54 (34)*	51	150 (20)	5.0-7.1 [41]
61 (10)	-29 (13)	25	61 (12)	
162 (9)	-8 (9)	-8	164 (14)	
48.0 (13.0)	-12.7 (10.4)*	8.2	45.1 (14.3)	6.5 [78]
30.0 (10.2)	-7.6 (9.8)		29.6 (10.6)	
9.2 (2.4)	-.7 (1.6)		9.0 (2.4)	

should be reported when using the DASH-DLV and PRWE-NL. The QuickDASH was validated in the Dutch language for patients with elbow dislocations [85], but not for patients with hand and wrist injuries. The MHQ has not been validated in the Dutch translated version. Our goal is to perform this in the near future. The SF-36 has been validated in the Dutch language in a general population and the authors concluded that it had acceptable validity [86]. However, statistically significant differences in mean scores were observed as a function of age, gender and the prevalence of chronic health conditions [86]. This supports our hypothesis that younger patients might score differently on PROs than older patients. To our knowledge, the SF-36 has not been validated in patients with hand and wrist injuries. The PROMIS Physical Function – Upper Extremity v2.0 (PROMIS UE v2.0) item bank, containing 46 items, was specifically designed for upper extremity disorders [87,88]. It has been translated to the Dutch language and validated (Chapters 7 and 8). We concluded that it measured a unidimensional trait. Following Item Response Theory, the Dutch-Flemish PROMIS UE v2.0 (DF-PROMIS-UE v2.0) item bank is now ready for Computer Adaptive Testing (CAT). CAT uses an algorithm that reduces the number of questions that need to be answered and therefore diminishes the burden for patients. In addition, the standard DF-PROMIS-UE v2.0 7-item short form consisting of 7 pre-determined questions showed sufficient psychometric properties. Age was not a determinant of outcome, i.e. younger patients did not answer items different than older patients. Patients with hand/wrist problems scored worse on items regarding fine tactile function, while patients with shoulder/ arm complaints scored worse on items regarding heavy lifting tasks. The impact on the total score, however, was negligible because the biases cancelled each other out. Our results from the validation studies suggest that outcome as measured with PROs might not necessarily be comparable between patient populations with different characteristics and with different disorders. In Chapter 7, we concluded that the construct validity of the DF-PROMIS-UE v2.0 was good with high correlations with all legacy instruments: DASH, PRWE and MHQ-ADL. This suggests that the DF-PROMIS-UE v2.0 could replace the more extensive PROs that have been validated in the Dutch language; the DASH-DLV and PRWE-NL. This might be promising for our suggested lean core set. The DF-PROMIS-UE v2.0 CAT or 7-item short form are also less time consuming, which is important for implementation in clinical practice. However, some differences in reliability between the PROs were found. The DASH and MHQ-ADL displayed better reliability than the DF-PROMIS-UE v2.0 standard CAT and 7-item short form. The MHQ-ADL was less reliable than the DF-PROMIS-UE v2.0 CAT and 7-item short form in patients with poor upper extremity functioning (Chapter 8). In addition, The DF-PROMIS-UE v2.0 CAT is on average more efficient than the DF-PROMIS-UE v2.o full item bank and 7-item short form and more efficient than the DASH, QuickDASH and MHQ (Chapter 8). This should be taken into account when interpreting these PROs in clinical practice. Because the PRWE was not administered in half of the population, we have not been able to perform reliability and efficiency analyses for the PRWE and PROMIS-UE v2.0 item bank, unfortunately. From our cohort studies, the MHQ seemed to provide more discriminative ability with substantial differences in scores between patients following DRFs with and without PA or in PLD/PLFD patients in comparison with healthy controls. For clinical practice, a reliable PRO with low burden for the patient is desirable, such as the MHQ-ADL, QuickDASH, PROMIS-UE v2.0 7-item short form and CAT methodology comprise of 7, 11, 7 and 4-7 items respectively.

If considering inclusion of a PRO in a 'lean' core set of measurements following hand and wrist injuries, the following should be taken into account: DASH and PRWE are PROs with an extensive number of items, which may be considered too much for use in daily clinical practice; MHQ has not been validated in the Dutch language yet and has no reported MICs for hand and wrist injuries; the translated version of the QuickDASH has not been validated for Dutch patients with hand and wrist injuries; the PROMIS-UE v2.0 item bank has no reported MICs yet. As such, it is not easy to advise on a lean version of a core set. For the time being, we advise to use the DASH and PRWE. We reconsider this advice if MICs have been determined for the PROMIS-UE v2.0 item bank and MHQ or if MHQ and QuickDASH have been validated in the Dutch translated versions for this specific patient cohort.

Minimal important change

Assessing patient progress has become an integral part of clinical practice nowadays. Meaningful threshold change values of outcome tools are essential for guidance and decisionmaking regarding a patient's treatment and rehabilitation strategies. Having clear values for MICs regarding PROs for hand and wrist injuries will facilitate clinical interpretation and optimal communication with individual patients regarding their outcome. The differences in PROs reported in this study between the healthy controls, patients following DRFs and patients following PLD/PLFDs are substantial and exceed reported MICs, indicating substantial impairments in daily life (Table 2). Note however that MICs are thresholds to determine clinical relevant changes as perceived in individual patients and not between groups. Terwee *et al*. state that interpretation of MICs should be done with caution due to different methodology and differences between patient cohorts [89]. Let us take a closer look at what we do know regarding MICs for the PRO scores reported in this thesis. Franchignoni *et al*. used a combination of anchor- and distribution-based methods to calculate the MIC for the DASH in 255 patients (mean age 49 years, SD 15) with upper extremity injuries of which 9% comprised of DRFs [43]. Walenkamp *et al*. calculated the MIC of the PRWE subscales and total scores on 102 Dutch patients (median age 59 years, IQR 48-66) following DRFs using anchor-based methods [44]. Shauver *et al*. used an anchor-based method to determine MIC of the MHQ for patients with carpal tunnel syndrome, reumatoid arthritis and DRFs [90]. The variation of the MICs for patients with carpal tunnel syndrome and reumatoid arthritis were substantial, supporting the theory that MICs should not be extrapolated between different patient cohorts. Due to ceiling effects for the DRF patients at the 3 months assessment, none of the MHQ domains showed discriminative ability [90]. Possibly this patient population was 'too good' to show discriminative ability and further research with larger populations is mandatory. For the SF-36, no MICs regarding upper extremity injuries have been calculated to our knowledge. We conclude that various methods have been used to determine MICs in literature, which might result in non-comparable MICs. In addition, MICs should not be extrapolated between different patient cohorts and therefore we hypothesize younger patients might have lower MIC thresholds to notice impairment. Further research is mandatory to determine clinical relevance in specific patient populations stratified for age and injury for all PROs reported in this thesis.

Strengths and weaknesses

One of the innovative aspects of this thesis is the specific inclusion criterium regarding age of the patient cohort. We have specifically tried to gain insight in a non-osteoporotic age group, since we believe they have high demands of the function of their hand and wrist following injury. The systematic review described in this thesis is the first to our knowledge to report on outcomes in this patient group.

Radiological measurements, CROs and PROs were concisely obtained with validated measurement protocols and are therefore reproducible. All radiographs were evaluated by a single radiologist specialized in musculoskeletal disorders with a special interest in hand and wrist anatomy; For CROs (aROM and grip strength) we used the same measurement protocol for all studies. For PROs we used the DASH, PRWE, MHQ and SF-36 for all cohort studies. As such, we produced manuscripts with specific information on a core set of CROs and PROs as have been suggested to report on when reporting on outcome following DRFs [80,81].

Table 2. Comparison of PROs of the studies of this thesis

PROs	DRF patients (N=73)	PLD/PLFD patients (N=11)	Mean difference DRF – PLD/ PLFDs	Healthy controls (N=22)	MIC
	Mean (SD)	**Mean (SD)**		**Mean (SD)**	
DASH	9 (12)	22 (20)	13	3 (6)	10.8 [43]
PRWE					
Pain	9 (11)	19 (14)	10	1 (2)	1.5 [44]
Function	10 (15)	19 (28)	9	0 (1)	10
Total	14 (17)	31 (22)	17	1 (3)	11.5
MHQ					
General function	74 (19)	59 (16)	15	94 (9)	
Activities general life	90 (15)	84 (13)	14	99 (2)	
Work	87 (21)	89 (20)	2	100 (0)	
Pain	85 (20)	71 (26)	14	98 (4)	
Esthetics	92 (15)	91 (11)	1	97 (11)	
Satisfaction	77 (26)	63 (30)	14	99 (2)	
Total	84 (16)	76 (15)	8	98 (3)	
SF-36					
Physical functioning	92 (12)	86 (9)	6	93 (15)	
Social functioning	90 (19)	80 (31)	10	95 (12)	
Role model physical problem	86 (28)	61 (41)	25	88 (30)	
Role model emotional problem	90 (27)	85 (35)	5	95 (21)	
Mental health	83 (13)	75 (19)	8	89 (11)	
Vitality	71 (18)	67 (21)	4	82 (15)	
Pain	81 (19)	68 (22)	13	90 (14)	
General health experience	73 (18)	67 (11)	6	78 (14)	
Health change	52 (20)	45 (10)	7	51 (14)	

n=number, PROs=patient reported outcomes, DRF=distal radius fracture, PLD/PLFD=perilunate (fracture) dislocation, MIC=minimal important change, DASH=disabilty of arm, shoulder and hand, PRWE=patient reported wrist evaluation, MHQ=michigan hand questionnaire, SF-36=short-form 36

Not only have we reported on statistical significance, but more importantly on clinical relevance by comparing outcomes with MICs as reported in literature. This has been scarcely performed in literature regarding hand and wrist injuries. Being able to extrapolate results as presented in this thesis to clinical practice is important. We believe we have contributed to clinicians' and patients' interpretation of CROs and PROs following hand and wrist injury in everyday clinical practice and this can guide treatment and rehabilitation strategies.

It has to be acknowledged that the included studies in the systematic review describe small cohorts of patients. In addition, the same is true for our clinical studies. Also, a selection bias may have been present in our clinical studies, since our respons rate was low. Conclusions regarding radiological measurements, CROs and PROs should therefore be interpreted with caution. Adequate sample sizes were used to validate the DASH-DLV, PRWE-NL and DF-PROMIS-UE v2.0. The reference values, error magnitudes and MICs reported in literature that we have used as references for CROs and PROs have been calculated mostly with (different) anchor based methods in small patient cohorts that are not completely comparable [31,41,43,44,78,90]. This implies care should be taken when drawing conclusions and further research is necessary.

Clinical implications

Most important knowledge for young non-osteoporotic patients and their primary treating clinicians is that flexion/extension and ulnar/radial deviation following DRFs and/or PLD/PLFDs have a high chance of being impaired to such an extent that patients will notice this in daily life. For patients following PLD/PLFDs these impairments seem to be worse than for patients following DRFs. Grip strength most likely is not affected for patients following DRFs (except those with radial shortening), but is clinically relevantly impaired in patients following PLD/PLFDs. Consequently, hand and wrist injuries can evolve in a major life event for a patient. At their visit to the surgical emergency department, it is therefore mandatory that patients receive adequate consultation and information regarding the characteristics of the injury and the expected outcomes. Following DRFs, PA and residual articular incongruency are main factors impacting range of motion and PROs. In addition, adequate correction of radial length seems important to decrease the risk of PA. Therefore, treatment strategies should be aimed at limiting articular incongruency to a minimum and correct radial length adequately in this patient population. Reference radiological measurements should be used with caution and we advise to use a radiograph of the uninjured wrist to put measurements in perspective and correct for anatomical variation.

Since hand and wrist injuries can evolve in major life events for patients, due to the possible impairment in daily life, we advise organisation of a specialized team dedicated to hand and wrist injuries including trauma surgeons, orthopaedic surgeons, plastic surgeons, rehabilitation physicians, radiologists and hand therapists. This multidisciplinary approach ensures the best possible primary treatment, but also facilitates optimal rehabilitation treatment to diminish future impairment to a minimum. In addition, it can help patients cope with residual diminished function and provide them with options for adjustments in daily life if needed.

For the individual patient it would be beneficial to get insight in their own progress following rehabilitation and in reference values of our suggested 'lean' core set of CROs and PROs from patients with a comparable age and injury. This way, a patient can gain realistic expectations of outcome following their hand and wrist injury. With actively involving individual patients in the treatment and rehabilitation process following an injury, this will add to achieving the best possible outcome.

Future perspectives

We would advise to create a database of non-osteoporotic patients following hand and wrist injury consisting of patient characteristics (i.e. age, gender, intensity of occupation, intensity of sports/hobbies), injury characteristics (i.e. type of injury, radiological measurements, open/closed injury, type of treatment) and CROs and PROs at several follow-up moments (baseline, 6 weeks, 3 months, 6 months, 1 year). Preferably, multicenter inclusion should be organized. Data should be collected in data repositories. The burden for patients and clinicians should be minimized. When patients consent to participating, most patient and injury characteristics can be retrieved from the digital patient system. Using an app or link for patients to fill in their missing patient characteristics (such as intensity of occupation and hobbies), using digital measurement systems for measuring CROs and using 'lean' PROs (for example the QuickDASH or PROMIS-UE v2.0 CAT or 7-item short) adds to diminishing the burden for patients. The database has multiple purposes.

Firstly, patients will be able to gain insight in their own progress during rehabilitation. Comparison to outcome reported for comparable patients from the database, puts outcome in perspective. For the treating clinician, this information can serve as a tool for transparent communication regarding expected outcome.

Secondly, the database can function as a quality registration. Annual reports on CROs and PROs of the included patients will enable transparency regarding differences in outcome between treating clinicians and centers.

Finally, with multicenter collection of data in the advised database, high quality research is possible. For example, calculating MICs of CROs and PROs for specific populations will be feasible. There is a need to determine the minimal change in a score that patients consider of importance for several outcome measures following hand and wrist injuries. We aim to calculate MICs regarding all CROs and PROs mentioned in this thesis for hand and wrist injuries in young non-osteoporotic patients.

Conclusions

We have aimed to put outcomes following hand and wrist injury in young non-osteoporotic patients in a clinically relevant perspective. PA had a relatively high prevalence following DRFs and progressed over time. Radiological measurements following DRFs evolved over time, but probably not with a clinical relevant impact within a follow-up period of five years. Diminished flexion/extension and ulnar/radial deviation is present following DRFs and PLD/PLFDs. Grip strength is clinically relevantly diminished in patients following PLD/PLFDs, but not in patients following DRFs. Associations between the presence of PA and diminished range of motion and diminished outcome on several PROs were present. Residual articular incongruency was associated with PA, diminished range of motion and possibly with diminished health status. Therefore, residual articular incongruence needs to be minimized by adequate reduction and (surgical) stabilization of DRFs to diminish the risk of development of PA in these young non-osteoporotic patients. Reported reference measurements do not seem to withhold clinical relevant thresholds. We suggest that measurements of the uninjured hand or wrist could be used to correct for anatomical variation. We conclude that the translated versions of the DASH, PRWE and PROMIS-UE v2.0 item bank have been adequately validated for Dutch patients with hand and wrist injuries. For clinical practice, we advise to use a 'lean' version of a core set of outcome measures; flexion/extension, ulnar/radial deviation and either the DASH or PRWE. In the future, after calculation of MICs, the PROMIS-UE v2.0 seems a promising tool to incorporate in this core set. We aim to validate the Dutch translated versions of the MHQ and SF-36 and to report on MICs for the DASH, QuickDASH, PRWE, MHQ, SF-36 and PROMIS-UE v2.0 item bank for young non-osteoporotic patients following hand and wrist injury. This will enable implementation of low burden PROs in 'lean' core sets to interpret outcome in clinical practice.

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CHAPTER 10

Summary

SUMMARY

Hand and wrist injuries are common in young non-osteoporotic patients and result mostly from high energy trauma. However, little emphasis has been put on reporting hand and wrist injuries in this specific young group with high demands of their hand and wrist and with a long active and working life ahead of them. Outcome following these injuries can be described using radiological measurements such as posttraumatic arthritis (PA), clinician reported outcomes (CROs) such as range of motion and grip strength, and patient reported outcomes (PROs) using questionnaires. Insight in the outcomes following hand and wrist injuries and the association between these different outcomes could guide treatment and rehabilitation strategies in this young non-osteoporotic patient category.

This thesis reported on several outcomes following hand and wrist injuries in young non-osteoporotic patients and puts these in a clinical perspective. **Part 1** described radiological measurements, CROs and PROs following distal radius fractures (DRFs) and perilunate (fracture) dislocations (PLD/PLFDs) in young non-osteoporotic patients. Furthermore, the association between these outcomes was analysed. **Part 2** explored the validity of several PROs that might be used to analyse consequences of hand and wrist injuries.

Part 1 (**Chapters 2 – 5**) of this thesis investigated the role of radiological measurements, CROs and PROs following DRFs and PLD/PLFDs and their interrelated associations. **Chapter 2** is a systematic review in which we provided an overview of literature on the association of PA with CROs and PROs in patients following DRFs who are of non-osteoporotic age. In addition, we aimed to present current knowledge on radiological predictors for PA. Prevalence of PA reported in all included studies was 50% and 37% when analysing the 10 studies with open source data. PA seemed to progress over time with a statistically significant higher prevalence of PA of 64% after follow-up > 36 months versus a prevalence of 31% with follow-up duration ≤ 36 months. Six studies described a statistical significant association between the presence of PA and diminished flexion/extension. From the open source data we calculated that the presence of PA was only related to a significantly diminished radial deviation. No association between PA and grip strength seemed to be present. No conclusions could be drawn regarding the impact of PA on PROs due to limited data. Only residual articular incongruency could be pointed out as a predictive factor for the development of PA.

In **Chapter 3** we explored the prevalence of PA and the association of PA with radiological measurements, CROs and PROs in a cohort of 73 young non-osteoporotic patients following DRFs with a median follow-up of 62 months. Also, we aimed to achieve insight in employment changes following DRFs. PA had a prevalence of 32% and was statistically significantly associated with longer radial length, diminished flexion/extension and ulnar/radial deviation. Grip strength

was not associated with the presence of PA. Regarding the PROs, multiple statistically significant associations with PA were found; the Michigan Hand Questionnaire (MHQ) subscales 'general functioning', 'esthetics', 'satisfaction' and the total score as well as Short-Form36 (SF-36) subscales 'physical functioning' were all worse for patients with PA compared to those without PA. In regression analyses the Disability of Arm Shoulder and Hand questionnaire (DASH), Patient Reported Wrist Evaluation (PRWE) subscale 'function' and the total score of the PRWE were statistically significantly associated with flexion/extension. Ten per cent of patients stopped working or changed occupation because of the sustained DRF.

In **Chapter 4** we compared the results of the radiological measurements of the same cohort of patients as described in Chapter 3 with error magnitudes and CROs and PROs with minimal important change (MIC) as reported in literature. In addition, associations between radiological measurements and outcomes were analysed. Although several radiological measurements evolved statistically significantly over time, none exceeded measurement errors. Regarding CROs following DRFs, flexion/extension, ulnar/radial deviation and pro/supination of the injured wrist were all significantly diminished compared to the uninjured wrist. Only MIC for flexion/extension and grip strength had been reported. The flexion/extension difference of 11.2° with the uninjured wrist exceeded MIC, while grip strength differences did not. MICs for DASH and PRWE have been reported in patients following DRFs, but not for MHQ nor for the SF-36 [1-3]. When comparing PROs in our population to PROs in healthy controls, the difference for the DASH did not exceed MIC, while the difference of the PRWE scores did. Furthermore, substantial differences between the DRF patients and healthy controls for MHQ subscales 'general function', 'work', 'pain', 'satisfaction' and total score and for SF-36 subscales 'vitality' and 'pain' were present. Unfortunately, no MICs have been published yet for the latter two PROs, which seems a shortcoming in interpreting these valuable outcome tools when reporting on hand and wrist injuries. Residual articular incongruency seemed to be associated with diminished range of motion. Also, a diminished SF-36 'mental component score' seemed to be statistically significantly associated with residual articular incongruency. Further research is mandatory on MICs when reporting outcome following DRFs, to be able to interpret clinically relevant outcomes.

Chapter 5 focused on PLD/PLFDs, which are rare injuries presented in nearly the same age group as those who sustained a DRF (Chapters 2, 3 and 4). To gain insight in the influence of PLD/PLFDs on outcome the 11 included patients in this cross-sectional study were matched to 22 healthy controls. Patients experienced a significant impact on every day life with diminished range of motion (flexion/extension and ulnar/radial deviation), pain, diminished physical functioning, diminished satisfaction and they reported a lower general health status than healthy controls. Interestingly, no consequences for work participation were found in this small study.

In **part 1** we emphasized that although several PROs are commonly used in reporting on outcomes following hand and wrist injuries, the interpretability and clinical relevancy are challenging. There is some variation in the psychometric properties of these instruments and the concepts measured are not always well defined. We think this might be due to insufficient validation for language and specific patient groups (target populations), but also due to a lack of knowledge on reference values, such as MICs for these instruments.

Therefore, in **part 2** (**Chapters 6 – 8**) of this thesis we focused on specific PROs used to report outcomes following hand and wrist injuries and the validation of these instruments for Dutch patients with upper extremity injuries. In **Chapter 6** we evaluated structural validity and construct validity using Confirmatory Factor Analysis (CFA) of the Dutch version of the DASH (DASH-DLV) for 370 patients with isolated hand or wrist injury. This study suggested that the DASH-DLV reflects a unidimensional trait. Thus, reporting on subscale scores is of very limited value and should be avoided. Further studies should asses the validity of the DASH-DLV in more detail, as well as other measurement properties to ensure reliable interpretation of this PRO in clinical practice.

The Dutch version of the PRWE (PRWE-NL) was previously validated by our research group using CFA and revealed that the PRWE-NL measures a unidimensional trait in Dutch patients with hand and wrist injuries [4]. This also suggests that a single score should be used for the PRWE-NL without reporting subscale scores.

As mentioned earlier, we face challenges in interpreting reported outcomes following hand and wrist injury with commonly used PROs due to variation in psychometric properties and measurements of unclearly defined constructs. In addition, completing (several) PROs is time-consuming for patients. Because of these challenges, the Patient-Reported Outcomes Measurement Information System (PROMIS) developed a series of item banks, including the PROMIS® Physical Function – Upper Extremity (UE) v2.0 [5,6]. The goal was to improve measurement quality, comparability of PROs across medical conditions and reduce patients' burden [7]. The item bank will be used as a Computerized Adaptive Test (CAT) system using an algorithm that selects questions from the item bank based on patients' response to previous questions. When a predefined precision is reached, the system automatically stops asking questions which reduces the number of questions that need to be asked.

In **Chapter 7** the Dutch-Flemish PROMIS UE v2.0 (DF-PROMIS-UE v2.0) item bank was validated in 303 patients with upper extremity injuries by reporting on structural validity and construct validity using CFA. We showed that the DF-PROMIS-UE v2.0 item bank measures a unidimensional trait. Sufficient structural validity, internal consistency and construct validity were found.

To be able to use the DF-PROMIS-UE v2.0 CAT, successful validation and calibration with Item Response Theory (IRT) needed to be conducted, which was performed in **Chapter 8.** In a cohort of 521 patients with upper extremity injuries, the assumptions for fitting an IRT model were considered to be met. Therefore, the DF-PROMIS UE v2.0 item bank is considered to show sufficient evidence for unidimensionality, had negligible local dependence, good Graded Response Model (GRM) fit and demonstrated sufficient measurement invariance. The DASH displayed better reliability than the DF-PROMIS-UE 7-item short form and standard CAT and the QuickDASH showed comparable reliability. The MHQ-ADL displayed better reliability than the DF-PROMIS-UE v2.0 7-item short form and standard CAT for T-scores between 28-50. For patients with low function, the DF-PROMIS-UE v2.0 measures performed better. In addition, The DF-PROMIS-UE CAT is on average more efficient than the DF-PROMIS-UE full bank and 7-item short form and more efficient than the DASH, QuickDASH and MHQ. The DF-PROMIS-UE v2.0 is now ready for use as CAT in research and clinical practice. CAT reduces the number of questions that need to be answered and therefore diminishes the burden for patients.

In **Chapter 9** we provided an overview of the research presented in this thesis. We have shown that hand and wrist injuries can evolve in major life events for patients, due to possible impairment in daily life. Therefore, for clinical practice, the organisation of a specialized team dedicated to hand and wrist injuries including trauma surgeons, orthopaedic surgeons, plastic surgeons, rehabilitation physicians, radiologists and hand therapists is advised. We propose a 'lean' version of the described core set of measures for clinical practice [8,9] with known MICs to interpret clinical relevant change; flexion/extension, ulnar/radial deviation and either the DASH or PRWE. Validation of the Dutch translated version of the MHQ and SF-36 was advices. In the near future, we aim to to report on MICs for the DASH, QuickDASH, PRWE, MHQ, SF-36 and DF-PROMIS-UE v2.0 item bank for young non-osteoporotic patients following hand and wrist injury. This will enable implementation of low burden PROs in 'lean' core sets to interpret outcome in clinical practice.

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APPENDICES

NEDERLANDSE SAMENVATTING

Letsels van de hand en pols komen vaak voor in jonge niet-osteoporotische patiënten en resulteren meestal van hoogenergetisch trauma. Toch heeft er weinig nadruk gelegen op het beschrijven van hand- en polsletsels in deze specifieke jonge groep met hoge eisen van hun hand en pols met een lang actief en werkend leven voor zich. Uitkomst na deze letsels kunnen worden beschreven aan de hand van radiologische metingen, zoals posttraumatische arthrose (PA) en clinician reported outcomes (CROs) zoals bewegingsuitslagen en grijpkracht. Daarnaast kunnen gevalideerde vragenlijsten in de vorm van Patient Reported Outcomes (PROs) worden gebruikt om uitkomst te rapporteren. Inzicht in de uitkomsten na hand- en polsletsels en de associatie tussen deze verschillende uitkomsten zouden richting kunnen geven aan behandel- en revalidatiestrategieën in deze jonge niet-osteoporotische patiëntcategorie.

Dit proefschrift beschreef verscheidene uitkomsten na hand- en polsletsels in jonge niet-osteoporotische patiënten en plaatst deze in klinisch perspectief. In **Deel 1** beschrijven we radiologische metingen, CROs en PROs na distale radius fracturen (DRFs) en perilunaire (fractuur) dislocaties (PLD/PLFDs) in jonge niet-osteoporotische patiënten. Bovendien is de associatie tussen deze uitkomsten geanalyseerd. **Deel 2** exploreerde de validiteit van verschillende PROs die kunnen worden gebruikt om de consequenties van hand- en polsletsels te analyseren.

Deel 1 (**hoofdstukken 2 – 5**) van dit proefschrift onderzocht de rol van radiologische metingen, CROs en PROs na DRFs en PLD/PLFDs en hun onderlinge associaties. In **hoofdstuk 2** presenteerden we een systematische review, waarin we een overzicht van de literatuur verstrekten aangaande de associaties van PA met CROs en PROs in patiënten na DRFs met een niet-osteoporotische leeftijd. In aanvulling hebben we getracht de actuele kennis ten aanzien van radiologische voorspellers van PA te presenteren. Prevalentie van PA gerapporteerd in alle geïncludeerde studies was 50% en 37% in de 10 studies met open source data. PA leek te verslechteren in de loop van de tijd met een statistisch significant hogere prevalentie van PA van 64% na een follow-up > 36 maanden in vergelijking met een prevalentie van 31% na een follow-up ≤ 36 maanden. Zes studies beschreven een statistisch significante associatie tussen de aanwezigheid van PA en verminderde dorsaal/palmairflexie. Van de open source data berekenden we dat de aanwezigheid van PA alleen gerelateerd was aan significant verminderde radiairdeviatie. Geen associaties tussen PA en grijpkracht leken aanwezig te zijn. Geen conclusies konden worden getrokken betreffende de invloed van PA op PROs door beperkte data. Alleen residuale articulaire incongruentie kon worden aangewezen als voorspellende factor voor het ontwikkelen van PA.

In **hoofdstuk 3** exploreerden we de prevalentie van PA en de associatie van PA met radiologische metingen, CROs en PROs in een cohort van 73 patiënten na DRFs met een mediane follow-up duur van 62 maanden. Ook hebben we getracht inzicht te verschaffen in werkgerelateerde veranderingen na DRFs. PA had een prevalentie van 32% en was statistisch significant geassocieerd met langere lengte van de radius, verminderde dorsaal/palmairflexie en ulnair/radiairdeviatie. Grijpkracht was niet geassocieerd met de aanwezigheid van PA. Met betrekking tot de PROs werden multipele statistische significante associaties gevonden; de Michigan Hand Questionnaire (MHQ) subschalen 'general functioning', 'esthetics', 'satisfaction' en de totale score alsmede de Short-Form36 (SF-36) subschaal ' physical functioning' werden allen slechter gescoord in patiënten met PA in vergelijking met patiënten zonder PA. In regressieanalyses bleken statistisch significante associaties te bestaan tussen de Disability of Arm, Shoulder and Hand questionaire (DASH), Patient Reported Wrist Evaluation (PRWE) subschaal 'function' en de totale score van de PRWE met dorsaal/palmairflexie. Tien procent van de patiënten stopten met werken of veranderden hun arbeidsaanstelling door de opgelopen DRF.

In **hoofdstuk 4** hebben we de resultaten vergeleken van de radiologische metingen in hetzelfde cohort als beschreven in hoofdstuk 3 te vergelijken met error magnitudes en CROs en PROs met minimal important change (MIC) zoals beschreven in de literatuur. Ook werden de associaties tussen radiologische metingen en uitkomsten geanalyseerd. Alhoewel meerdere radiologische metingen statistisch significant veranderden in de loop van de tijd, overtrof geen enkele meting error magnitudes. Aangaande CROs na DRFs waren dorsaal/palmairflexie, ulnair/radiairdeviatie en pro/supinatie van de aangedane pols allemaal significant verminderd in vergelijking met de niet-aangedane pols. Alleen de MIC voor dorsaal/palmairflexie en grijpkracht is beschreven in literatuur. Het verschil in dorsaal/palmairflexie tussen de aangedane en niet-aangedane pols van 11.2° overtrof de MIC, terwijl het verschil in grijpkracht dit niet deed. MICs voor de DASH en PRWE zijn gerapporteerd in patiënten die een DRF doormaakten, maar niet voor de MHQ of de SF-36. Wanneer de PROs in onze populatie werden vergeleken met PROs van gezonde vrijwilligers, overschreed het verschil voor de DASH niet de MIC, terwijl het verschil in scores voor de PRWE dat wel deed. In aanvulling werden substantiële verschillen gezien tussen de DRF patiënten en gezonde vrijwilligers voor de MHQ subschalen 'general function', 'work', 'pain', 'satisfaction' en totale score. Hetzelfde gold voor de SF-36 subschalen 'vitality' en 'pain'. Helaas zijn er geen MICs gepubliceerd voor de laatste twee PROs, wat een tekortkoming lijkt als het gaat om het interpreteren van deze waardevolle meetinstrumenten bij het rapporteren over hand- en polsletsels. Residuale articulaire incongruentie leek geassocieerd te zijn met verminderde bewegingsuitslagen. Ook leek een verminderde SF-36 'mental component score' statistisch significant geassocieerd te zijn met residuale articulaire incongruentie. Meer onderzoek is nodig naar MICs bij het presenteren van uitkomst na DRFs om klinisch relevante uitkomsten te kunnen interpreteren.

Hoofdstuk 5 was gericht op PLD/PLFDs; zeldzame letsels die voorkomen in een vergelijkbare leeftijdsgroep als de groep die we beschreven na een DRF (Hoofdstukken 2, 3 en 4). Om inzicht te verkrijgen in de invloed van PLD/PLFDs op uitkomst werden de 11 geïncludeerde patiënten gematched met 22 gezonde vrijwilligers. Patiënten ervoeren een significante invloed op hun dagelijks leven met verminderde bewegingsuitslagen (dorsaal/palmairflexie en ulnair/radiairdeviatie), pijn, verminderd fysiek functioneren, verminderde tevredenheid en ze rapporteerden een lagere algemene gezondheidsstatus dan de gezonde vrijwilligers. Interessant genoeg werden er geen consequenties voor de invulling van hun arbeidsaanstelling gevonden in deze kleine groep.

In **deel 1** hebben we benadrukt dat alhoewel verscheidene PROs veelvuldig gebruikt worden bij het rapporteren van uitkomst na hand- en polsletsels, de interpretatie en klinische relevantie van deze instrumenten uitdagend zijn. Er bestaat variatie in de psychometrische eigenschappen van deze instrumenten en de concepten die gemeten worden zijn niet altijd duidelijk gedefiniëerd. We denken dat dit mogelijk komt door insufficiënte validatie voor taal en specifieke patiëntgroepen (target populaties), maar ook door een lacune in kennis ten aanzien van referentiewaarden, zoals MICs voor deze instrumenten.

Daarom hebben we in **deel 2** (**hoofdstukken 6 – 8**) de nadruk gelegd op specifieke PROs die gebruikt worden om uitkomst te rapporteren na hand- en polsletsels en de validatie van deze instrumenten voor nederlandse patiënten met bovenste extremiteitenletsels. **Hoofdstuk 6** was gericht op het evalueren van structurele validiteit en construct validiteit, waarbij gebruikgemaakt werd van Confirmatory Factor Analysis (CFA) van de nederlandse versie van de DASH (DASH-DLV) voor 370 patiënten met geïsoleerde hand- en polsletsels. Deze studie suggereerde dat de DASH-DLV een unidimensionale trait bezit. Dus het rapporteren van subschalen heeft geen meerwaarde en zou moeten worden vermeden. Toekomstige studies moeten de validiteit van de DASH-DLV in meer detail onderzoeken, alsmede ander meeteigenschappen om een betrouwbare interpretatie van deze PRO in klinische setting te waarborgen.

De nederlandse versie van de PRWE (PRWE-NL) werd al eerder gevalideerd door onze onderzoeksgroep, waarbij gebruik werd gemaakt van CFA en hierbij bleek dat de PRWE-NL ook een unidimensionale trait bezit in nederlandse patiënten met hand- en polsletsels. Dit betekent dat ook bij deze PRO één score moet worden gebruikt zonder het rapporteren van subschalen.

Zoals eerder werd vermeld, is het uitdagend om gerapporteerde uitkomsten te interpreteren na hand- en polsletsels met veelgebruikte PROs doordat er variatie in psychometrische eigenschappen bestaat. Ook zijn de constructs van de PROs niet altijd duidelijk omschreven. Daarnaast is het zo dat het beantwoorden van (meerdere) PROs is een tijdrovende bezigheid. Door deze tekortkomingen, ontwikkelden de Patient-Reported Outcomes Measurement

Information System (PROMIS) een aantal item banks, waaronder de PROMIS® Physical Function – Upper Extremity (UE) v2.0. Het doel was om de meetkwaliteit te verbeteren, vergelijkbaarheid van PROs bij patiëntgroepen met verschillende medische condities te waarborgen en het verlagen van de belasting voor de patiënt. De item bank zal worden gebruikt als een Computerized Adaptive Test (CAT) systeem welke een algoritme gebruikt dat vragen selecteert van de item bank gebaseerd op de respons van de patiënt op voorgaande vragen. Als een vooraf gedefiniëerde precisie is bereikt, stopt het systeem automatisch met vragen stellen wat het aantal benodigde vragen reduceert.

In **hoofdstuk 7** hebben we de nederlands-vlaamse PROMIS UE v.20 (DF-PROMIS-UE v2.0) item bank in 303 patiënten met bovenste extremiteitenletsels gevalideerd door te rapporteren over structurele validiteit en construct validiteit, waarbij gebruik gemaakt wordt van CFA. We toonden aan dat de DF-PROMIS-UE v2.0 item bank een unidimensionale trait bezit. Sufficiënte structurele validiteit, interne consistentie en construct validiteit werden gevonden.

Om de DF-PROMIS-UE v2.0 te gebruiken, moet er succesvolle validatie en calibratie met Item Response Theory (IRT) worden uitgevoerd. Dit werd verricht in **hoofdstuk 8.** In een cohort van 521 patiënten met bovenste extremiteitenletsels werd aan de aannames voldaan om te passen binnen een IRT model. Hierdoor is het zo dat de DF-PROMIS-UE v2.0 item bank voldoende bewijs leverde voor unidimensionaliteit, ze verwaarloosbare lokale afhankelijkheid had (local dependence), goed paste in een Graded Response Model (GRM) en ze demonstreerde sufficiënte meetinvariantie (measurement invariance). De DASH had betere betrouwbaarheid (reliability) dan de DF-PROMIS-UE v2.0 short form en standaard CAT en de QuickDASH toonde vergelijkbare betrouwbaarheid. De MHQ-ADL toonde betere betrouwbaarheid dan de DF-PROMIS-UE v2.0 short form en standaard CAT voor T-scores tussen 28-50. Voor patiënten met een slechte functie, presteerde de DF-PROMIS-UE v2.0 beter dan de eerder genoemde PROs. Aanvullend bleek de DF-PROMIS-UE v2.0 CAT gemiddeld efficiënter te zijn dan de DF-PROMIS-UE v2.0 volledige item bank en de 7-item short form. Daarnaast was de DF-PROMIS-UE v2.0 CAT ook efficiënter dan de DASH, en MHQ. De DF-PROMIS-UE v2.0 is nu klaar om gebruikt te worden als CAT voor onderzoeksdoeleinden en in de klinische praktijk. CAT reduceert het aantal vragen dat gesteld moeten worden en verminderd daardoor de belasting voor patiënten.

In **hoofdstuk 9** gaven we een overzicht van het onderzoek dat verricht is in dit proefschrift. We hebben aangetoond dat hand- en polsletsels kunnen evolueren in majeure 'life events' voor patiënten, door de mogelijke invaliditeit in het dagelijks leven. Voor de klinische praktijk adviseerden we daarom de organisatie van een gespecialiseerd team toegewijd aan hand- en polsletsels waarin traumachirurgen, orthopedisch chirurgen, plastisch chirurgen, revalidatieartsen, radiologen en handtherapeuten vertegenwoordigd kunnen zijn. We stellen een 'lean' versie voor van de beschreven basisset van metingen om te gebruiken in de kliniek met bekende MICs om relevante veranderingen te objectiveren: dorsaal/palmairlexie, ulnair/radiairdeviatie en de DASH of PRWE. Daarnaast adviseren we dat de nederlandse versie van de MHQ en SF-36 wordt gevalideerd. In de nabije toekomst stellen we ons tot doel om MICs voor de DASH, QuickDASH, PRWE, MHQ, SF-36 en DF-PROMIS-UE v2.0 item bank te presenteren voor jonge niet-osteoporotische patiënten na hand- en polsletsel. Dit zal bijdragen aan het kunnen implementeren van PROs met lage belasting in 'lean' basissets, waardoor de uitkomst na hand- en polsletsels in de klinische praktijk beter kan worden geïnterpreteerd.

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Lieve Erben en Jonas, jullie zijn ons grootste geluk en de hoogste prioriteit in het leven, altijd.

CURRICULUM VITAE

Charlotte Marijke Lameijer werd op 7 november 1983 geboren in Sassenheim, als oudste dochter van Rinus en Jolanda. Ze groeide op met haar broer Bart en zus Renée in Sassenheim, Roden en Altena. Op het Augustinus College te Groningen haalde ze in 2002 haar atheneum diploma.

In september 2002 begon zij haar studie Geneeskunde aan de Rijksuniversiteit Groningen. In 2003 haalde ze haar propodeuse. Charlotte heeft haar coschappen in het Tjongerschans ziekenhuis te Heerenveen en het Medisch Centrum te Leeuwarden gelopen. Het keuze-coschap Traumachirurgie heeft ze gedeeltelijk in het St. George Hospital in Sydney te Australië en gedeeltelijk in het Universitair Medisch Centrum Groningen gedaan. Haar afstudeerscriptie deed ze bij de afdeling Traumachirurgie in het Universitair Medisch Centrum Groningen naar perilunaire luxaties en –luxatiefracturen.

Na het behalen van haar artsexamen in april 2009 is Charlotte als ANIOS Heelkunde begonnen, waarna ze startte met de opleiding Heelkunde in september 2010. Tot september 2013 vond dit plaats in het Medisch Centrum Leeuwarden. In deze periode begon ze ook met haar promotietraject op de afdelingen Revalidatiegeneeskunde en Traumachirurgie onder leiding van prof. dr. Corry K. van der Sluis en prof. dr. Henk Jan ten Duis. Van september 2013 tot september 2014 vervolgde ze haar opleiding in het Universitair Medisch Centrum Groningen, waarna haar eerste jaar differentiatie Traumachirurgie in het Isala ziekenhuis te Zwolle volgde tot 1 september 2015. Van 1 september 2015 tot 1 januari 2016 volgde Charlotte een fellowship Visceral Trauma in het Groote Schuur ziekenhuis te Kaapstad onder leiding van prof. dr. Andrew J. Nicol. Op 1 september 2016 rondde ze haar opleiding tot traumachirurg af in het Universitair Medisch Centrum Groningen.

Van 2013 tot en met 2016 gecombineerde ze haar opleiding en promotie met een functie als AIOS-bestuurslid van de Nederlandse Vereniging voor Traumachirurgie.

Van september 2016 tot september 2018 volgde ze een fellowship Traumachirurgie in het Amsterdam UMC, locatie VUmc. Hierna werd ze aangenomen als staflid, alwaar ze nog werkzaam is.

Charlotte is instructeur voor de cursussen Advanced Trauma Life Support (ATLS) en Definitive Surgical Trauma Care (DSTC). Voor de Nederlandse Vereniging voor Traumachirurgie houdt ze zich bezig met de organisatie en invulling van het landelijke traumachirurgisch onderwijs voor AIOS Heelkunde (CASH) en de visie op de toekomst van de traumachirurg in de werkgroep 'Profiel Traumachirurg 2020-2022'. Ook is ze betrokken bij de organisatie van de nationale AO Young Generation Seminars en het jaarlijks terugkerend AO minisymposium op de Chirurgendagen.

Charlotte is getrouwd met Huub en ze hebben samen twee prachtige zonen; Erben en Jonas.