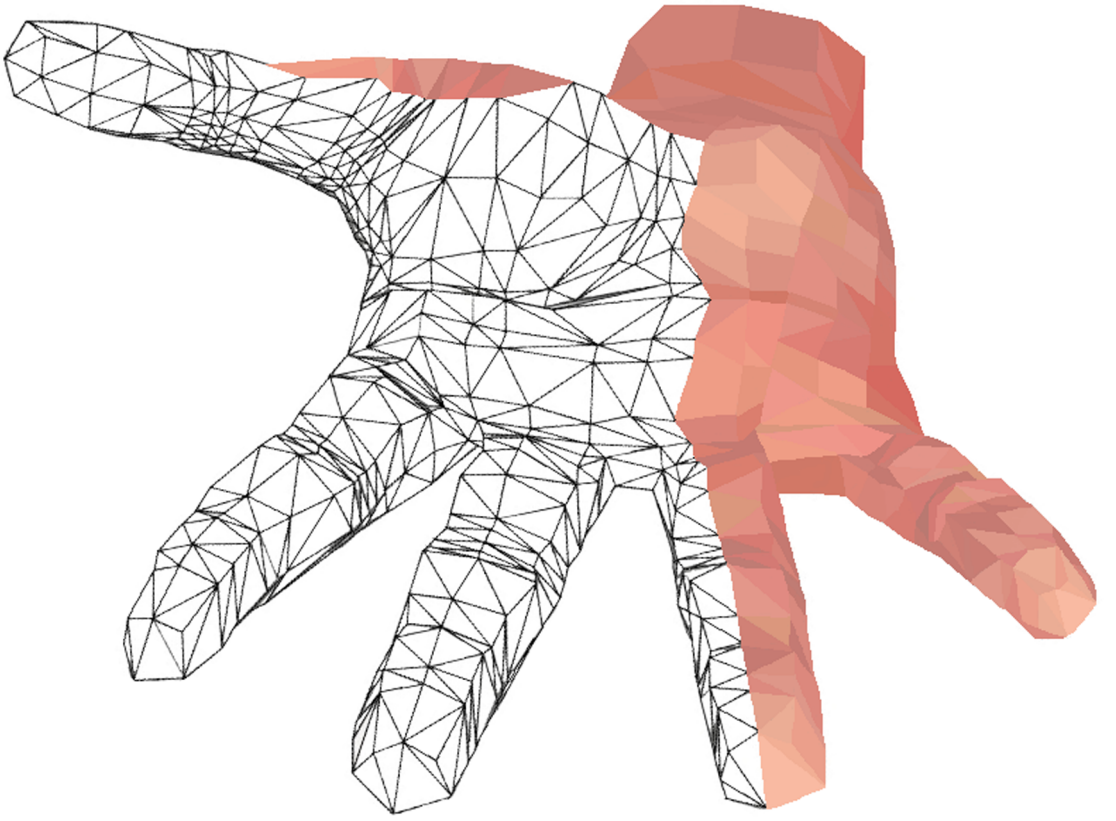

Dissecting Carpal Tunnel Syndrome through Statistical Modelling

Factors influencing treatment outcomes

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Dissecting Carpal Tunnel Syndrome through Statistical Modelling

Factors influencing treatment outcomes

Het carpaal tunnel syndroom ontleden door middel van statistische modellen

Factoren die de behandeluitkomsten beïnvloeden

Proefschrift

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1 | General introduction and outline of this thesis

GENERAL INTRODUCTION

1. Pathophysiology

1.1 Primary CTS

Carpal tunnel syndrome (CTS) is a condition caused by the entrapment of the median nerve between the transverse carpal ligament and the carpal bones[1]. The function of the median nerve consists of both the sensational innervation of the thumb, index finger, middle finger, and half the ring finger, as well as the motoric innervation of the muscles of the base of the thumb. Furthermore, the median nerve is located in the carpal tunnel of which the floor and sides are formed by the carpal bones and the roof is formed by the transverse carpal ligament. Multiple structures pass through the carpal tunnel such as the median nerve and nine flexor tendons that control flexion of the fingers.

From literature, multiple causes[1–3] of CTS have been suggested. For example, repetitive movements of the wrist might lead to thickening of the synovial lining of the tendons that lie in the carpal tunnel. This results in an increased volume of tissue in the carpal tunnel which leads to compression of the median nerve[4,5]. Subsequently, this mechanical pressure on the median nerve leads to ischemic changes to the median nerve which results in impaired function[2]. Moreover, it is thought that chronic compression of the median nerve breaks down the blood-nerve barrier which leads to endoneurial and subperineurial edema of the median nerve[2]. This edema can be seen as one of the MRI findings in patients with carpal tunnel syndrome[1,6]. In addition, it is hypothesized that because of this edema, the perineurium and epineurium thicken and become fibrotic, impairing the function of the nerve[2]. Other MRI findings that are reported for patients with CTS consist of flattening of the median nerve, and palmar bowing of the transverse carpal ligament[6,7]. However, in clinical practice, the diagnosis of CTS is often mentioned as idiopathic. Therefore, more research on examining the pathophysiology of idiopathic CTS and the improvement of additional testing methodology in the clinical setting might lead to better identification of subgroups of CTS patients, based on different pathophysiologies. This may then lead to more tailored approaches for the treatment and prevention of CTS.

It has been shown that the amount of pressure in the carpal tunnel is of great importance for the occurrence of deterioration of the median nerve[8–10]. The normal amount of pressure in the carpal tunnel lies around 2 to 10 mmHg when the wrist is in a neutral position[11]. However, the amount of pressure in the carpal tunnel is dependent on different factors and could increase around eightfold when fully flexing the wrist and tenfold when fully extending the wrist[5]. It has been shown that the pressure in the carpal tunnel in a neutral position for patients with CTS is usually around 30 mmHg[12,13]. Therefore, pressure even increases more greatly in CTS patients when flexing and extending the wrist. Based on animal models, *Lundborg et al.*[14] and *Rydevik et al.*[15] found that an increase of pressure in the canal to 20-30 mmHg in neutral position results in decreased venous blood flow of

the median nerve. Subsequently, a pressure of around 50 mmHg decreases arterial flow and edema can be observed. At a pressure of 80 mmHg, complete nerve ischemia is likely to occur.

It has been hypothesized that the decrease of nerve venous blood flow is important in the pathogenesis of CTS, because this might lead to the accumulation of blood and leads to edema and hyperaemia of the nerve which further increases the pressure in the carpal tunnel[16]. Fortunately, non-surgical treatment or surgical treatment in the form of a carpal tunnel release (CTR) is often able to reduce the pressure in the canal to normal levels to prevent irreversible damage to the median nerve[17].

While previous studies have focused on the relation between pressure and nerve deterioration in animal studies[14,15], still little is known on the mechanisms underlying the damaging of the median nerve due to increased pressure and recovery of the median nerve. Therefore, future studies could focus more in-depth on these mechanisms to have a better understanding of the role of carpal tunnel pressure in the pathophysiology of CTS which may lead to better treatment and prevention of CTS. In addition, the efficacy and mechanisms of both prevention and treatment strategies could be analysed on the cellular level in future (animal) models as well.

1.2 Recurrent and persistent CTS

While treatment for CTS is in general effective in relieving symptoms, in some cases treatment might not be successful and recurrent or persistent CTS symptoms can occur. The definition of recurrent CTS is often described as the recurrence of symptoms after a period in which symptoms were absent[18,19]. However, no consensus on the amount of time that symptoms need to be absent is present in literature. Furthermore, persistent CTS refers to the persistence of symptoms after treatment or acute recurrence of symptoms within a short period[18,19]. In literature, the rate of recurrence and persistent symptoms for CTS in large series has been estimated around 5%[18–20]. When patients were treated surgically for their primary CTS, the most important cause of persistent symptoms was an incomplete release of the transverse carpal ligament during the primary surgery[21]. Moreover, when CTS patients present with new or worse CTS symptoms after surgical treatment, iatrogenic nerve injury should be considered. It has been estimated that some extend of iatrogenic nerve injury can be found in 3%-6% of secondary surgeries for CTS[18,21].

Other common causes of persistent or recurrent symptoms are the median nerve being tethered in scar tissue or the presence of circumferential fibrosis around the median nerve[18,21,22]. In addition, hypertrophic tenosynovitis is also found to be related to the occurrence of recurrent or persistent symptoms, because proliferation due to the tenosynovitis increases pressure in the carpal tunnel[23]. Moreover, systemic conditions such as diabetes mellitus, thyroid pathology, and hypertension might also be associated with an increased risk for developing recurrent or persistent complaints after treatment for primary CTS[24].

However, still, the underlying pathophysiology of recurrent or persistent carpal tunnel syndrome is unclear and far less is known on the mechanisms underlying the occurrence of secondary CTS than there is for the occurrence of primary CTS. More insights into the mechanisms behind secondary CTS could lead to improvement of treatment and prevention. Although there are multiple different treatment techniques for the treatment of secondary CTS, it is not clear which technique gives the best treatment outcomes. More insights in the different pathophysiologies of the occurrence of secondary CTS might also give more insights on which treatment is best suitable, based on the underlying cause of the secondary CTS.

2. Epidemiology

It has been stated that the prevalence of CTS in the general population is around 7% in people between 18 and 75 years of age[25,26]. From literature, multiple factors have been described to be associated with an increased risk for the occurrence of CTS. For example, gender, age, BMI, work-related factors, diabetes mellitus, rheumatoid arthritis, thyroid pathology, and genetic predisposition have been suggested to be associated with an increased risk for CTS[27–32].

Considering gender, women tend to have around a threefold higher risk of CTS compared to men[33,34]. This might partially be explained by the influence of hormones on carpal tunnel syndrome. For example, *Kaplan et al.*[35] showed that women with CTS have had a higher number of pregnancies and hypothesized that pregnancy-related hormonal changes may have long-term effects that increase the incidence of CTS in women. This could be explained by the presence of estrogen receptors in the transverse carpal ligament and the tenosynovium of the flexor tendons that effects tissue composition[36].

Considering age, studies reported a higher prevalence of palmar bowing of the transverse carpal ligament with higher age[37]. It has been stated that people with an age above 40 years have an odds ratio (OR) of 1.9 compared to people younger than 40[34]. Although age has been described as an independent factor for the risk of CTS, it also plays an important role in the interaction between factors. For example, an interaction between BMI and age has been described in the literature[34,38,39]. This interaction is so that a BMI higher than 30 has a greater effect in younger age groups (age<30)(OR=4.81) then it has on older age groups (age>30)(OR=1.51)[38]. It has been hypothesized that, because of the increasing rate of obesity in developed countries, the prevalence of CTS might also increase especially in relatively young people[38].

BMI as an independent factor is associated with 2.5 times higher risk for the occurrence of CTS in individuals with a BMI higher than 29, compared to individuals with a BMI below 29[40]. It has been thought that an increased BMI could lead to CTS because of the increased amount of fat in the carpal tunnel and therefore also increased fluid retention[40].

From literature, multiple work-related factors have been mentioned to be of influence for the risk of CTS[41–43]. In general, the most important job-related factors for the occurrence of CTS are high levels of hand vibration, prolonged work with a flexed or extended wrist, high requirements of hand force, and repetitiveness of certain movements[44]. Because of these factors, some specific occupations have an increased risk for CTS such as assembly workers[45–47] and rock drillers[48].

Multiple systemic conditions have been related to an increased risk for the development of CTS, such as diabetes mellitus, rheumatic diseases, and thyroid pathology. Considering diabetes mellitus, a meta-analysis by *Pourmemari et al.*[49] found an OR of 1.97 for the association between diabetes mellitus and CTS. In addition, the risk of developing CTS for a patient with diabetes mellitus increases with longer duration of the diabetes mellitus[50]. *Singh et al.* estimated that the lifetime risk for developing CTS when suffering from type 1 diabetes mellitus is around 85%[50]. A proposed mechanism for the occurrence of CTS in patients with diabetes mellitus is that diabetes mellitus leads to glycosylation of collagen fibres in the carpal tunnel and this way stiffens the fibres. Because of this decreased compliance of the fibres, the pressure in the carpal tunnel increases[51]. Furthermore, another hypothesis is that high glucose levels in the blood lead to elevated glucose levels in the median nerve as well because of the diffusion of glucose through the blood-nerve barrier. This results in endoneurial edema which can result in compression of the median nerve[52].

Considering rheumatoïd arthritis, it has been shown that the inflammatory reactions that arise with rheumatoid arthritis can lead to anatomical changes of the carpal tunnel, leading to a higher risk for CTS[53]. A meta-analysis by *Pourmemari et al.* found an OR of 1.96 between rheumatoid arthritis and the occurrence of CTS[54].

From the literature, it has been hypothesized that thyroid pathology may lead to accumulation of mucopolysaccharides in the soft tissue around the median nerve which may lead to compression[55]. A meta-analysis by *Shiri et al.*[56] showed an OR of 1.32 when looking at the pooled effect from studies that did not adjust for confounding. However, when analysing the studies that did adjust estimates for confounding, this association disappeared.

Last, the occurrence of CTS is not only dependent on environmental factors, but might also be largely explained by genetic factors. A twin study by *Hakim et al*. showed that the occurrence of CTS is up to 50% dependent on genetic components[57]. This is in line with the hypothesis that the risk of occurrence of CTS is dependent on genetic variants between people such as variants for the interleukin, collagen, and growth factor hormone genes[58,59]. From literature, clear hereditary types of CTS in families have been described as well[31,60,61].

While multiple studies have found separate factors associated with the occurrence of CTS in the population, still little is known about the interaction between these factors. Therefore, the influence of these factors is largely only interpretable on a population scale. By studying the interaction between these separate different factors by, for example, creating prediction models for the individual risk of the occurrence of CTS, a better predic-

tion for individual people could be made to identify the risk of occurrence of CTS. Future research could then also focus more on how these factors could be used to improve the prevention of CTS. For example, these factors could be used to improve identification of high-risk patients and, this way, improve the cost-effectiveness of prevention methods by being able to make a better selection of people likely to benefit from preventive measures.

3. Symptoms and diagnosis

3.1 Symptoms

The most common symptoms related to CTS are paresthesia, dysesthesia, and pain in the distal distribution of the median nerve (thumb, index finger, middle finger and the radial side of the ring finger)[62]. Symptoms of CTS tend to worsen at night, waking up patients from their sleep[63]. To improve symptoms, CTS patients often describe the typical 'flick sign' which is the phenomenon that shaking or flicking the wrist relieves symptoms[64]. Furthermore, in severe cases of CTS, atrophy of the thenar muscle and loss of motor function such as grip strength are present due to axonal degeneration[65]. Moreover, a study by *Padua et al.* showed that there are differences in the reported symptoms between patients with mild to moderate CTS and severe CTS[65]. They showed that patients with mild to moderate CTS were more likely to report more severe symptoms such as paresthesia, dysesthesia, and pain, but also reported low functional impairment. In contrast, for patients with more severe CTS, the symptoms are often milder because of the substantial nerve damage that has already established, while these patients experience severe functional impairments[65].

Furthermore, still little is known on the presence of certain subgroups of CTS patients based on the type of symptoms patients experience. Therefore, future research could focus on identifying any subgroups of patients based on symptom presentation in large databases. More information on if these kinds of subgroups exist could lead to a more tailored approach for treatment options and could be of influence for managing expectations for treatments and therefore improve satisfaction after treatment.

3.2 Diagnosing CTS

The diagnosis of CTS is a clinical one that can be supported by the use of specific tests. Two common provocative tests for CTS are the Phalen's and Tinel's test. When performing the Phalen's test, patients are asked to keep their wrist in a flexed position for 60 seconds. This test is positive if the patient experiences paraesthesia or pain in the distribution of the median nerve[66]. Although the sensitivity and specificity for the Phalen's test vary in the literature, the overall estimate for the sensitivity and specificity for the Phalen test has been estimated at 68% and 73%, respectively.

Furthermore, the Tinel's test is performed by tapping on the volar side of the wrist. This test is positive if the tapping is provocating paraesthesia or pain in the distribution of the median nerve[67]. The overall estimate for the sensitivity and specificity for this test has been

estimated at 50% sensitivity and 77% specificity[68]. The sensitivity and specificity for both the Phalen's and Tinel's test vary between studies, possibly because of the discrepancies between the method of examination and interpretation of results between examiners[2].

For the diagnosis of CTS, multiple diagnostic tests have been suggested. First, the added value of electrodiagnostic testing for CTS is debated[69,70]. In general, electrodiagnostic testing for CTS has a low and strongly variable sensitivity(49%-84%) and high specificity(95-100%)[69,71]. In the clinical setting, this would mean that patients without symptoms of CTS are not likely to have abnormal electrodiagnostic results and that a substantial proportion of patients with symptoms of CTS will have normal electrodiagnostic results as well. Therefore, electrodiagnostic testing is not recommended for standard diagnostic testing or as an indicative factor for surgery[70]. In addition, for patients in which CTS has been diagnosed based on physical examination and medical history, electrodiagnostic testing does not hold any additional value[69]. However, in some cases where the clinical diagnosis of CTS is not clear, electrodiagnostic testing may be of additional value[70].

Second, ultrasound might be used for additional testing. With ultrasound, swelling and flattening of the median nerve in the carpal tunnel with bowing of the flexor retinaculum can be found in CTS patients[70,72]. The reported sensitivity and specificity for the use of ultrasound for diagnostic testing differ greatly between studies[73]. In general, the sensitivity and specificity for the use of ultrasound for the diagnosis of CTS are estimated at 77.6% and 86.8%, respectively[73]. The use of ultrasound can be of additional value especially when high-resolution ultrasound is used[74]. Moreover, ultrasound in the combination with electrodiagnostic testing might be of additional value for patients in which the clinical diagnosis of CTS is not clear[75–77].

Third, magnetic resonance imaging(MRI) can be of additional for special diagnostic problems such as carpal tunnel syndromes which do not respond adequately to conservative or surgical treatment[78]. MRI can then be used to rule out more rare pathological causes of CTS such as ganglion, haemangioma or bony deformity[79].

While CTS remains mainly a clinical diagnosis, this might change with the improvement of imaging and electrodiagnostic testing techniques in the future. Also, better diagnostic algorithms and clinical prediction rules could support clinical decision making by physicians when diagnosing CTS. These algorithms and clinical prediction rules could approach the diagnosis of CTS as a probability rather than a binary outcome[80]. This could decrease the difficulty of diagnosing CTS which could then, for example, decrease referral rates to relatively expensive hand specialists by general practitioners. However, the benefit and cost-effectiveness of these approaches of diagnosing CTS should be examined in future research.

4. The Boston Carpal Tunnel Questionnaire

A widely used questionnaire to evaluate and monitor the symptoms and function of CTS patients in clinical practice and research is the Boston Carpal Tunnel Questionnaire (BCTQ)[81]. This questionnaire consists of two domains, the symptom severity scale (SSS) to assess the severity of symptoms of CTS patients, and the functional status scale (FSS) to assess the functional status of CTS patients. The SSS and FSS consist of eleven and eight questions respectively. Patients answer the questions on a Likert scale from 1 to 5, based on how severe or often they experience the condition mentioned in the question, where 1 means no complaints of the condition mentioned in the question and five means severe complaints of the condition mentioned in the question. From these questions, an average score for the SSS and FSS can be calculated which results in a score between 1 and 5, where a score of 1 means no CTS complaints and 5 means severe CTS complaints.

The BCTQ has shown te be a valid, reliable, responsive and acceptable measurement tool[82]. However, it has also been shown that questionnaire length and low patient-perceived content validity of the questionnaire might be burdensome for patients and that response burden is negatively correlated with a reduction in response rate[83]. Therefore, diminishing response burden of the BCTQ can be beneficial, especially in clinics where patients are asked to fill in multiple questionnaires at frequent time points. Because of this, one of the aims of this thesis was to create an electronic decision tree version of the BCTQ to diminish questionnaire length of the BCTQ with a minimum loss of measurement properties and this way decrease response burden for patients with CTS.

5. Treatment options for CTS

5.1 Non-surgical treatment

Multiple non-surgical treatment options are available for the treatment of CTS such as splinting/bracing, hand therapy and exercises, and injections[84]. First, splinting/bracing is used to prevent extremes in flexion or extension and this way prevents peak pressures in the carpal tunnel. The use of a nocturnal brace is in general more effective in treating symptoms of CTS and improving hand function compared to no nocturnal brace[85]. Although the nocturnal use of the brace improves symptoms and function for patients with CTS, there is no evidence for an additional effect of full-time use of a wrist splint compared to night-only use in patients with CTS in the short term[86]. Furthermore, no differences in symptoms and function for patients with CTS were found between the use of a wrist splint or a brace[87].

Second, tendon and nerve gliding exercises are often recommended for patients with CTS because this could stretch the median nerve and prevent adhesions in the carpal tunnel. In addition, because of the ‘milking’ mechanism of these exercises, these exercises might reduce tenosynovial edema and improve the venous return from the nerve[88,89]. Although little evidence is available on the effectiveness of gliding exercises, gliding might

be a complementary option to accelerate recovery of function[89–91] and to improve grip strength[92].

Last, the use of corticosteroid injection for patients with CTS might be beneficial to reduce the chronic synovial inflammation that is often present with CTS. This way, swelling of the flexor synovial is reduced and pressure in the carpal tunnel can be decreased[93]. While the treatment of CTS with corticosteroid injections results in significantly greater symptom relief compared to the use of a placebo[94], beneficial effects are often seen only in the short term. For example, *Green et al.* reported a median duration of corticosteroid injections of 3.3 months on the reduction of symptoms for CTS patients[95]. Therefore, on the long-term, often surgical decompression is needed[96].

Still, it is relatively unknown which patients are likely to benefit from non-surgical treatment options for CTS and which patients will not. Better identification of patients who are likely to benefit or are likely not to benefit from non-surgical treatment beforehand would be beneficial and could make CTS treatment more cost-effective and could reduce the risk for patients of getting ineffective treatments or unnecessary surgeries.

5.2 Surgical treatment for primary CTS

While conservative treatment may be more suitable for mild and short-term cases of CTS, surgical treatment of CTS in the form of a CTR is in general more effective than conservative treatment in treating CTS and should be considered when symptoms are persistent[97]. However, the risk of complications should be taken into account as they are more severe with surgical treatment. Furthermore, because of the high prevalence in the general population, it has been estimated that around 1.9% of men and 4.1% of women undergo a CTR during their lifetime[28]. The CTR is performed by cutting the transverse carpal ligament to increase the space in the carpal tunnel and reduce pressure in the carpal tunnel. Although the reported success rates of CTR differs greatly between studies, the general success rate in relieving symptoms for the CTR has been estimated to be around 75% in literature[98]. While surgical treatment of CTS is effective in general, still it is difficult to predict outcomes for individual patients. On the individual level, some predictive factors have been described that are predictive for the postoperative outcomes for CTS patients. For example, successful reduction of symptoms is less likely in patients with severe CTS and older than 60 years of age compared to younger patients with severe CTS symptoms[99,100]. In addition, some studies mention the presence of comorbidities such as DM to be predictive for worse postoperative outcomes[101]. However, the predictive value of the presence of DM for the outcome after CTR is debated in the literature[93,102]. Also, relief from steroid injection has been described as a predictor for better outcomes of surgical treatment of CTS[103].

Moreover, the consumption of alcohol(more than two drinks per day) and smoking of cigarettes are predictive for worse functional outcomes and more severe symptoms after CTR[104]. Furthermore, a longer duration of CTS symptoms is associated with a decreased

risk for complete nerve recovery[105,106], however, this association is debated in literature as well[107,108]. Because CTS leads to high economic costs worldwide both direct and indirect[109], the return to work after a CTR is also considered as an important outcome. From literature, multiple factors are associated with the return to work after a carpal tunnel release such as hand intensive work[110], receiving workers compensation[111], gender[111], and duration of preoperative sick leave[112].

Although multiple studies report different factors that might be associated with the outcome after CTR, almost no studies have combined these factors in a prediction model from a large database to improve the prediction of outcome for individual patients. Therefore, one of the aims of this thesis was to create multiple prediction models from large databases to improve the prediction of individual treatment outcomes.

5.3 Surgical treatment for recurrent CTS

Multiple surgical techniques have been described for treating recurrent CTS including revision decompression[113–115], autologous fat transfer[116], resurfacing of the median nerve with a hypothenar fat pad flap[113,117] and pedicled flaps[118,119] all with variable results[113–119]. However, little comparative research on reported outcomes between different surgical techniques for recurrent CTS has been conducted. Therefore, it is not clear which surgical technique provides the best outcome for recurrent or persistent CTS, while there are big differences in invasiveness between techniques. Because of this, one of the aims of this thesis is to provide more insights into the difference in postoperative outcomes for the treatment of recurrent CTS.

6. Psychological factors influencing treatment outcomes

The influence of psychological patients factors such as disease perception, pain catastrophization, and mental health on surgical outcomes is becoming a more important topic in literature in the past years[120]. Considering illness perception, a widely used measurement tool to quantify illness perception is the Illness Perception Questionnaire(IPQ)[121]. In general, illness perception is often divided into different components of illness perception based on the Leventhal's Self-Regulatory Model[122]. These components consist of the perception of illness on identity, the perception of the consequences of the illness on daily life, perception of the illness timeline, perception of illness control, and perception of the cause of illness. Since the development of this model of illness perception, illness perception has been studied for a wide range of conditions such as heart diseases[123,124], rheumatoid arthritis[125,126], cancer[127,128], chronic obstructive pulmonary disease[129], and diabetes[130]. In addition, the influence of illness perception on treatment outcomes has shown te be of importance for multiple conditions such as renal diseases[131,132], asthma[133], and musculoskeletal diseases[134]. However, little still little is know on the influence of illness perception on the reported treatment outcomes by CTS patients while this could lead to

low-cost interventions to improve patient-reported outcomes. In addition, more information on the influence of illness perception on treatment outcomes for CTS could lead to the identification of patients who are of higher risk for postoperative dissatisfaction.

Considering pain catastrophization, this is defined as a negative cognitive-affective coping response to anticipated or actual pain[135] that has been associated with pain-related outcomes. In addition, pain catastrophization can be divided into three components: rumination ("I can't stop thinking about how much it hurts"), magnification ("I'm afraid that something serious might happen"), and helplessness ("There is nothing I can do to reduce the intensity of the pain)[136]. In literature, it has been shown that pre-surgical assessment of pain-catastrophization of patients is an important predictor for the amount of postoperative pain[137]. However, little is known about the effect of pain catastrophizing on the patient-reported outcomes after CTR.

Considering the mental health status of a patient, It has been shown that a pre-operative worse mental health state is associated with a lower postoperative satisfaction rate after CTR[138,139]. Furthermore, an association between mental health status and symptom severity has been described in the literature[139,140]. *Shin et al*.[140] showed that by improving the mental health status of CTS patients, the symptoms of CTS also decreased. Moreover, *Khan et al.*[141] stated that the subjective symptoms of CTS of patients correlate better with psychological patient factors than with electrodiagnostic testing. In addition, psychological patients factors might be associated with other treatment outcomes such as the return to work after a CTR as well[110,142].

It is becoming more clear that prehabilitation for surgery does not only need to prepare patients physically for surgery but also mentally[143]. However, more research on this association for the CTR and CTS specific is needed. Therefore, one of the aims of this thesis was to provide more information on the association between psychological patient factors and treatment outcomes of CTS patients.

THESIS OUTLINE

This thesis contains three parts containing the proposed aims of this thesis.

Part 1: Collecting treatment outcomes from carpal tunnel syndrome patients

In **Chapter 2,** the answer patterns within the BCTQ in relation to the total score of the BCTQ is examined by applying the CHAID algorithm. By doing so, a decision tree version of the widely used BCTQ is created to decrease the response burden for CTS patients in research and clinical setting to fill in the BCTQ.

Part 2: Factors influencing treatment outcome after surgical treatment of primary carpal tunnel syndrome

In **Chapter 3** we will create a prediction model with the aim to improve the prediction of postoperative outcomes for individual CTS patients six months after a CTR. In **Chapter 4** we will examine the relation between surgeon-volume of the CTR procedure and the post-operative treatment outcomes of CTS patients. In **Chapter 5** we will look at the Influence of illness perceptions, psychological distress and pain catastrophizing on self-reported treatment outcomes in patients with CTS. Likewise, in **Chapter 6** we will examine the influence of illness perception and mental health on the return to work after a CTR.

Part 3: Factors influencing treatment outcome after surgical treatment of secondary carpal tunnel syndrome

In **Chapter 7**, I will compare the outcomes of the surgical treatment of primary CTS and secondary CTS patients in a propensity score-matched study cohort. In **Chapter 8**, we will create a prediction model to improve the individual prediction of postoperative outcomes for patients with recurrent or persistent CTS. Because it is unclear if there are differences between surgical techniques for the treatment of recurrent CTS, we will compare treatment outcomes from the literature of different surgical techniques for the treatment of recurrent CTS in **Chapter 9**.

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PART I

COLLECTING TREATMENT OUTCOMES FROM CARPAL TUNNEL SYNDROME PATIENTS

2 | Item Reduction of the Boston Carpal Tunnel Questionnaire Using Decision Tree Modeling

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ABSTRACT

Objective: The aim of this study is to produce an electronic decision tree (DT) version of the Boston Carpal Tunnel Questionnaire (DT-BCTQ) using the Chi-squared automatic interaction detection (CHAID) algorithm to reduce questionnaire length of the Boston carpal tunnel questionnaire (BCTQ) while minimizing the loss of measurement properties. **Design:** Criterion standard study. All BCTQ's completed between January 2012 and September 2016 by patients who were treated for carpal tunnel syndrome (CTS) were randomly divided into a development and a validation dataset at a three-to-one ratio. Optimization of the CHAID-algorithm was performed in the development dataset to determine the most optimal DT-BCTQ. **Setting:** Private hand clinic providing both surgical and non-surgical (orthosis and exercise therapy) treatment for hand and wrist disorders. **Participants:** 4470 CTS patients completed a total of 10055 BCTQ's. **Interventions:** Not applicable. **Main outcome measures:** The intraclass correlation coefficient (ICC) was calculated between the original BCTQ-scores and the scores predicted by the DT-BCTQ in the validation dataset. Bland-Altman plots visualized the agreement between the BCTQ and the DT-BCTQ. **Results:** The DT-BCTQ reduced the number of questions needed to ask a patient from 11 to a maximum of 3 for the symptom severity scale (SSS) domain and from 8 to maximally 3 for the functional status scale (FSS) domain. The ICC between the original BCTQ and DT-BCTQ was 0.94. The mean difference between the BCTQ and DT-BCTQ was 0.05 on the 0-5 scale(CI= -0.48, 0.57) for the SSS, 0.02 (CI= -0.45, 0.49) for the FSS and 0.04 (CI= -0.31, 0.39) for the total BCTQ-score. **Conclusion:** By creating the DT-BCTQ, we diminished the number of questions needed to ask a patient from 18 to a maximum of six questions, three for each subscore, when administering the BCTQ while maintaining an ICC of 0.94 with the original BCTQ.

Keywords: Carpal Tunnel Syndrome, Surveys and Questionnaires, Decision Trees

List of abbreviations

PROM	Patient reported outcome measure
CTS	Carpal tunnel syndrome
BCTQ	Boston Carpal Tunnel Questionnaire
SSS	Symptom severity scale
FSS	Functional status scale
IRT	Item response theory
CHAID	Chi-squared Automated Interaction Detection
ICC	Intra class correlation
DT-BCTQ	Decision tree version of the Boston Carpal Tunnel Questionnaire
CAT	Computer adaptive testing

INTRODUCTION

In modern patient-centred healthcare, the patient experience of disease is increasingly important in both clinical practice and research[1]. To assess patient experience of disease, patient-reported outcome measurements (PROMs) are frequently employed for monitoring disease[2], improving quality of care[3] and as primary outcomes in clinical research[4].

Within the field of hand surgery, a widely used PROM to assess the severity of carpal tunnel syndrome(CTS) is the Boston Carpal Tunnel Questionnaire(BCTQ)[5] also known as the Levine questionnaire. The BCTQ is often utilized as a primary outcome measure in clinical CTS research[6-8] and is herein the most commonly-used standardized measure to assess symptom severity[9]. Although the BCTQ has been found to be a reliable, responsive and acceptable instrument[10], it has also been shown that questionnaire length and a low patient-perceived content validity of the questionnaire might be burdensome for patients and that response burden is negatively correlated with a reduction in response rate[11]. In addition, diminishing response burden of multiple PROMs can be beneficial, especially in clinics where patients are asked to fill in multiple questionnaires at frequent timepoints. In PROM research, reducing questionnaire length while maintaining robust psychometric properties is frequently proposed[12-17]. Regarding the BCTQ, a six-item version of the SSS-domain of the BCTQ was developed by applying exploratory factor analysis and item response theory (IRT) analysis of the original SSS[17].

A method that is particularly suitable for reducing item length of electronic questionnaires is Chi-squared Automated Interaction Detection (CHAID). CHAID is a non-parametric method to automatically detect interactions between categorical variables in large datasets[18] and is commonly applied in marketing research[19]. CHAID is able to construct a decision tree from the questionnaire items based on the discriminatory power of individual items and classifies data based on the interaction between dependent and independent factors. In this way, the CHAID-algorithm is able to recognize answer patterns within a questionnaire and their relation to the total score. It is called a decision tree as after a first question is presented, based on the score for this item, the most discriminative next question is presented, which can be different for each score for the first question. This pattern can be repeated until a sum score is reliably calculated. The CHAID technique has already been successfully applied to reduce item length of multiple assessments within the medical field[20-22]. For example, the CHAID algorithm was successfully used to shorten the Prodromal Questionnaire for routine screening for psychosis from 92 to only 16 items while maintaining similar sensitivity and specificity for identifying patients with psychosis[20].

The aim of this study was to determine answer patterns within the BCTQ in relation to the total score by applying the CHAID-algorithm. In doing so, an electronic decision-tree version of the BCTQ could be produced to diminish questionnaire length of the BCTQ with a minimum loss of measurement properties.

METHODS

Measurements

To assess the severity of CTS symptoms and functional status, patients filled out the BCTQ (Dutch Language Version[23]) at baseline, six weeks, three months and six months of treatment. The BCTQ covers two domains - the symptom severity scale (SSS) and the functional status scale (FSS), including 11 and eight items respectively. Every item consists of five answer options, ranked in terms of severity of the complaint and translating to a score from 1 to 5. The domain subscores are then calculated by taking the average of the scored items. For this study, all completed questionnaires at all different timepoints (intake, six weeks, three months and six months) were used for the analysis. Furthermore, we collected baseline characteristics from all patients, such as gender, age and type of treatment, consisting of conservative or surgical treatment and primary or recurrent treatment. In addition, we recorded the duration of completion of the BCTQ.

Patient selection

For this study, we utilized data from patients who were treated either surgically with a carpal tunnel release or conservatively with a splint between January 2012 and September 2016 at one of the clinics of Xpert Clinic. Xpert Clinic is a specialized clinic providing both hand therapy and surgery for wrist- and hand complaints. Patients were diagnosed with CTS by a physician based on the combination of symptoms, physical examination findings and electrodiagnostic testing. In addition, patients were asked by email to complete the BCTQ for the treated hand in our web-based outcome registration system at intake, six weeks, three months and six months after treatment. In the case of patients who underwent multiple CTS treatments, only the first treated hand was included in this study. Patients were selected if they completed the BCTQ at least once. As all items of the BCTQ had to be completed by the patients to be submitted electronically, we had no missing items in each BCTQ. The data employed in this study was collected during routine outcome measurement and all patients supplied their consent for anonymized use of their data. This study was approved by the institutional review board of the Erasmus MC. Further, we adhered to the STROBE-guidelines.

Decision-tree development

All completed BCTQ questionnaires were randomly divided into a development and validation dataset at a three-to-one ratio by computerized randomisation with the statistical program, R. The BCTQ questionnaires within the development dataset were employed to optimize and select a decision tree and the validation dataset was utilized to test the external validity of the selected decision trees.

In the development dataset, two decision trees were created, one for the SSS and one for the FSS subdomain score. As a first step, the CHAID-algorithm determined the item of the subdomain with the best discriminative power for that subdomain score, defined as the item for which the subdomain score differed most between the various answer options. Next, the CHAID-algorithm placed the most discriminative item at the start of the decision tree and then split all the completed questionnaires into subgroups based on the answer given for that item. Thereafter, within these subgroups, the CHAID-algorithm would again identify the most discriminative item and split that subgroup into smaller subgroups based on the answer options of that item. Splits were performed only when the subdomain scores of the grouped questionnaires for a specific answer option were significantly different (p-value < 0.05) from the subdomain scores of the subgroups for the other answer options of that specific item. This process continued until stop conditions were met, which depended on the settings of the parameters minimal split, minimal bucket and maximal depth of the decision tree, of the CHAID-package in R[24]. In our case, the minimal split referred to the minimal number of BCTQ questionnaires needed to be present in a subgroup for the algorithm to seek a subsequent split within that subgroup. The minimal bucket is defined as the minimal number of questionnaires necessary to end in a subgroup after splitting. Lastly, maximal depth is defined as the maximum amount of subsequent splits allowed to be performed and ranges from 2 to 4. When stop conditions are met, an end group ('terminal node') is created. Subsequently, a score will be predicted for each terminal node. Therefore, the end result of executing the CHAID-algorithm is a decision tree that classifies answer patterns within questionnaires and is able to predict the domain scores based on the terminal node where the subject ends.

In the development dataset, we determined the optimal decision tree for a domain of the BCTQ by calculating the difference between the original scores and scores predicted by the decision tree for each possible decision tree. From this, we computed the mean and standard deviation (SD) of these differences for each decision tree and manually selected the decision tree with the best trade-off between a low SD and low depth (number of subsequent splits). The chosen decision tree BCTQ (DT-BCTQ) was then validated within the independent validation dataset.

Decision-tree validation

Within the independent validation group, we compared the final DT-BCTQ with the original BCTQ by performing two analyses. First, we created Bland-Altman plots to evaluate the amount of agreement between the predicted scores by the DT-BCTQ and original BCTQ. Secondly, the mean difference and variability in the difference between the predicted and original scores were calculated. Lastly, we computed the ICC between the predicted domain scores from the DT-BCTQ with the original scores of the BCTQ. All analyses were performed using R version 1.0.143, with the R studio interface using the CHAID package[24].

RESULTS

Patient selection

A total of 10055 BCTQ questionnaires were completed between January 2012 and September 2016 by 4470 patients. Subsequently, 7541 and 2514 questionnaires were randomly selected for the development and validation datasets, respectively. The patient characteristics for these datasets can be observed in Table 1. The average age of all included patients was 53.5 ± 13.4, 87% received surgical treatment and 90% received primary treatment. The average SSS, FSS and total BCTQ score was 2.26 ± 0.85, 2.12 ± 0.84 and 2.19 ± 0.79, respectively.

Table 1. Characteristics of the patients who completed the BCTQ questionnaires, with the n for the amount of completed BCTQ questionnaires assigned to each dataset.

		Development Dataset (n=7541)	Validation Dataset (n=2514)
Categorical variables		**%**	**%**
Gender	Women	73	70
Treatment	Conservative	13	11
	Surgical	87	89
	Primary	90	89
	Recurrent	10	11
Age	<30	5	6
	30-40	11	10
	40-50	19	18
	50-60	34	34
	60-70	20	20
	>70	11	13
Continuous variables		**Mean ± SD**	**Mean ± SD**
BCTQ-score	Total	2.17 ± 0.79	2.15 ± 0.77
	FSS	2.11 ± 0.84	2.09 ± 0.83
	SSS	2.24 ± 0.84	2.21 ± 0.82
		Median (Q1-Q3)	**Median (Q1-Q3)**
Duration of completion of the BCTQ		167 (121-243)	167 (122-243)

Decision-tree development

The SD of the difference between the predicted and original SSS-score ranged from 0.23 to 0.38 on a 1-5 scale for all decision trees, depending on maximal depth and minimal bucket size. For the FSS-score, this ranged from 0.21 to 0.34. A maximum depth of 2 resulted in higher SD's while a maximal depth of 3 resulted in similar SD's as a maximal depth of 4. In addition, a larger minimal bucket resulted in higher SD's for the difference between

the predicted and original score. Therefore, we selected the final decision tree for the SSS domain with a maximal depth of 3 and the most optimal minimal bucket size setting of 10. This resulted in a decision tree for the SSS domain with a SD of the difference between the predicted and original SSS score of 0.25. Likewise, we chose a decision tree for the FSS domain with a maximal depth of 3 and the optimal setting of a minimal bucket size of 25. This resulted in a decision tree for the FSS domain with a SD of the difference between the predicted and original FSS score of 0.24.

The final decision trees for the SSS and FSS domains are presented in Supplementary Figures 1 and 2. Viewing these figures, all possible paths through which a patient is able to answer the decision trees are visualized, which results in 67 and 59 different paths within the DT-SSS and DT-FSS domains, respectively, with a maximum of three questions posited per domain. In addition, we published an online version of the DT-BCTQ that is openly available (https://personeel.equipezorgbedrijven.nl/ls/index.php?r=survey/index&sid=824633&lang=nl)[25].

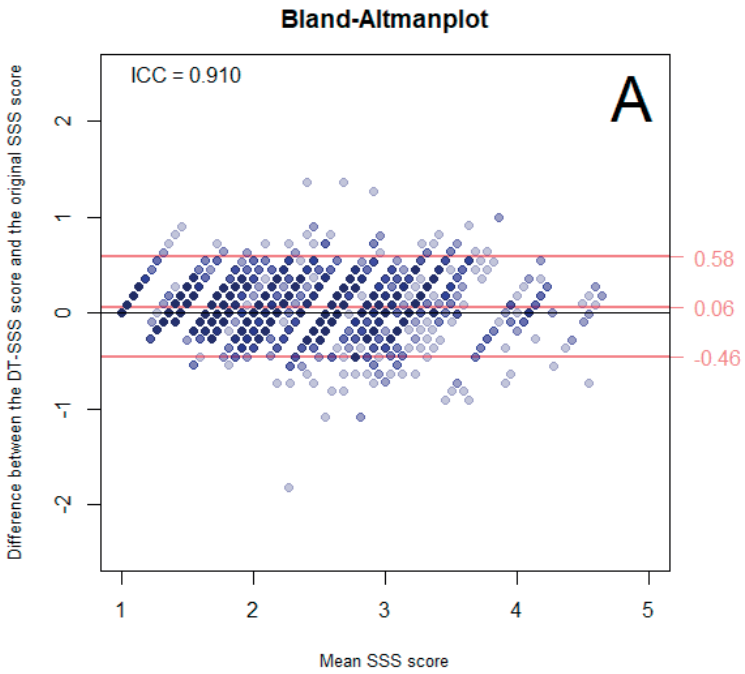

Figure 1 *(continued on next page)*

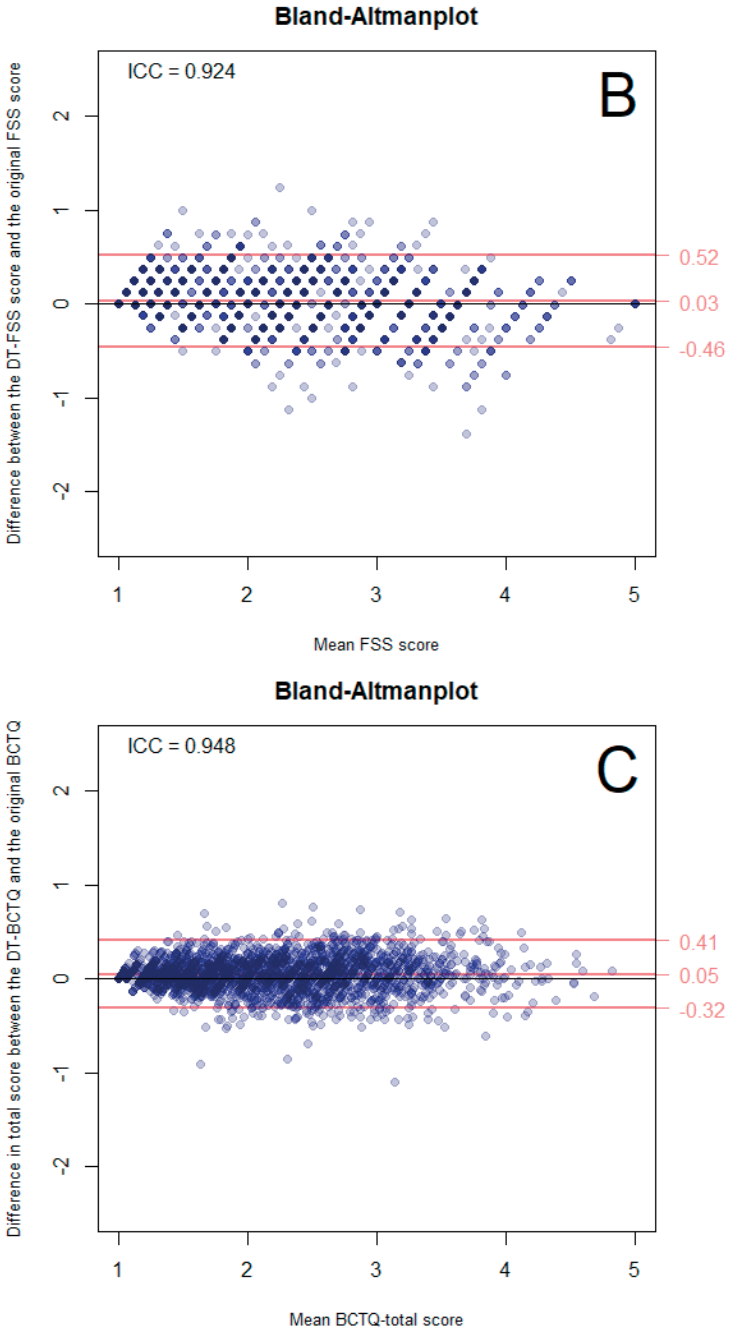

Figure 1A-C. Bland-Altman plots displaying the agreement between the original BCTQ and the DT-BCTQ for the SSS(figure 1A), the FSS(figure 1B), and the total BCTQ-score(figure 1C). In addition, the ICC between the original BCTQ and the DT-BCTQ is given for the total BCTQ-score and the two separate domains. Darker points represent a higher frequency of data for that point.

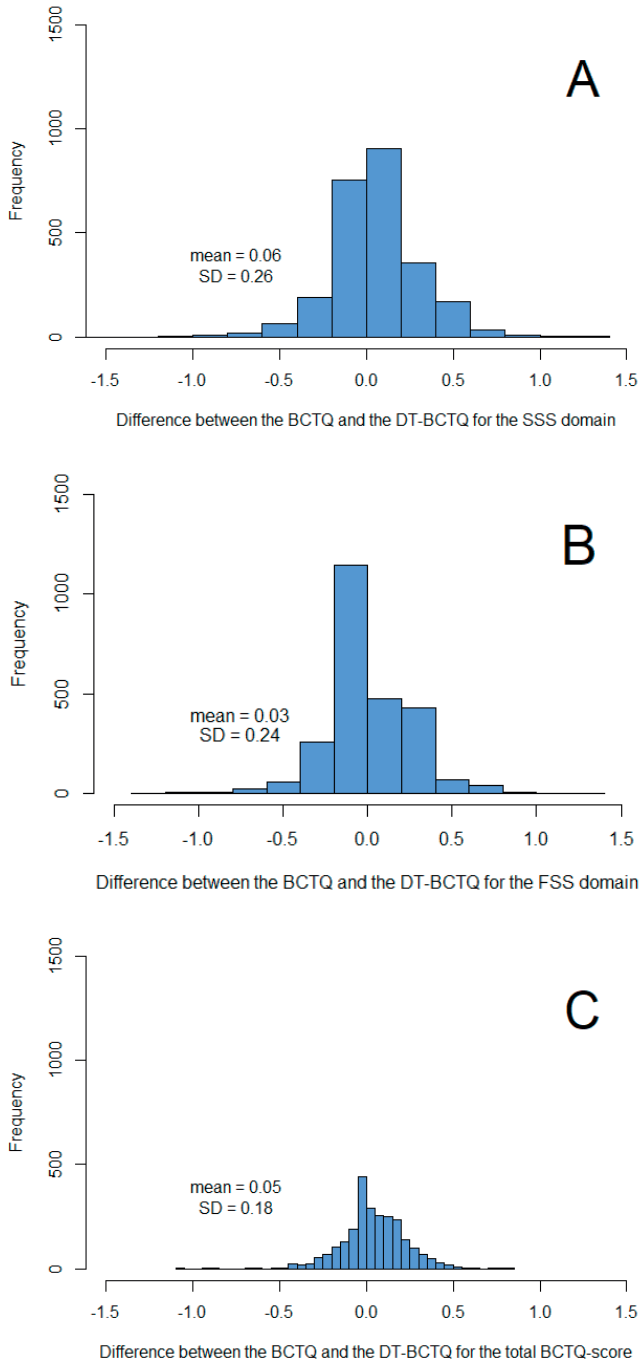

Figure 2A-C: Distributions of the differences between the original BCTQ and the DT-BCTQ for the SSS (figure 2A), the FSS (figure 2B) and the total BCTQ-score (figure 2C).

Decision-tree validation

Figure 1A-C depicts the Bland-Altman plots for the difference between the predicted scores by the selected decision trees and original score for the SSS, FSS and total score within the validation dataset. The mean difference between the DT-SSS and original SSS was 0.06 (CI= -0.64 to 0.63) on a 1-5 scale (Figure 1A). The mean difference for the FSS-domain was 0.03(CI= -0.46 to 0.52) (Figure 1B). Lastly, the agreement of the total BCTQ score had a mean of 0.05 (CI= -0.32 to 0.41) (Figure 1C). In addition, the distributions of the differences between the original and predicted scores by the selected decision trees for the SSS, FSS and total BCTQ score are visualized in Figure 2A-C. Furthermore, the predicted scores for the SSS, FSS and total BCTQ had an ICC with the original scores of 0.91 (CI= 0.87-0.94), 0.92 (CI= 0.89-0.96) and 0.95 (CI= 0.94-0.96), respectively.

DISCUSSION

By analyzing the patterns through which the BCTQ was completed, applying the CHAID algorithm, we were able to reduce the total amount of questions of the BCTQ needed to pose to a patient to assess the severity of CTS from 18 to maximally six questions, three for each subscore, while maintaining a high amount of agreement (ICC of 0.94) with the original BCTQ in our independent validation dataset.

Although the BCTQ is a widely used questionnaire to assess symptom severity in daily clinical practice and clinical research, no study has previously attempted to reduce item length for both domains of the BCTQ. Atroshi et al.[17] developed a six-item version of the SSS domain of the BCTQ by using exploratory factor analysis and item response theory (IRT) analysis, which resulted in an ICC of 0.80 with the original 11-item SSS. Furthermore, no previous studies have reported item diminution for the FSS and total score of the BCTQ yet.

By employing approximately 10.000 completed BCTQ questionnaires in the construction of the decision-tree version of the BCTQ, we were able to construct decision trees for the two domains of the BCTQ with an ICC of 0.91-0.92. We included multiple questionnaire from patients when available because in this specific analysis we were interested in recognizing patterns in item response. The purpose of this evaluation was to investigate the internal correlations between the questions of the BCTQ and total score. The algorithm carries this out by analyzing the distribution of answers for the different questions in relation to the total score[18]. While some patients completed multiple questionnaires, this was at different timepoints (baseline, early and later after treatment), which may result in differences in item response and therefore permits the algorithm to better detect these patterns. Moreover, because this study had access to a large amount of completed BCTQ questionnaires, large development and validation datasets could be built that allowed

the CHAID-algorithm to reliably predict BCTQ scores while greatly reducing the amount of questionnaire items necessary. Furthermore, because of the large datasets that were utilized to develop the decision trees, our results are likely to be generalizable to other CTS populations as well.

Study Limitations

An important limitation of this study is that we simulated how patients would fill in the DT-BCTQ based on their response to the original BCTQ. It is possible that the responses to the DT-BCTQ might be different from those of the original BCTQ because the items are not posed in the same sequence. While computerized administration of health status assessments in the form of, for example, decision-tree modelling or computer adaptive testing (CAT) can be beneficial, these methods also have disadvantages. For example, patients must be willing to accept the electronic version of the questionnaire and a higher degree of technological facilities are needed[26]. Seeing the DT-BCTQ is a fully electronic questionnaire, it will be difficult to implement it in practices with limited access to online technology. An advantage of a CHAID-based decision tree is that the tree is fixed and therefore technically easier to apply compared to CAT which continuously needs to calculate the next-best question based on the previously administered questions, requiring specific CAT software and often slowing down the processes of presenting a next question to the patient.

Furthermore, additional studies are required to evaluate the psychometric properties of the DT-BCTQ, such as the test re-test reliability and validity. As well, although the agreement between the DT-BCTQ and original BCTQ scores is high, results from the DT-BCTQ to measure severity of CTS complaints might not be entirely comparable to the findings of previous studies employing the original BCTQ.

Although the item reduction of the BCTQ might save patients only a limited amount of time, in clinical practice, often several additional questionnaires are presented to a patient, such as a quality of life questionnaire and patient-reported experience measure. Therefore, decreasing the length of each specific questionnaire can still be clinically relevant to diminish the total burden for the patient and increase response rates. Additionally, because each individual patient will receive the most relevant questions from the BCTQ based on their responses, the DT-BCTQ might improve patient-perceived content validity and could therefore also bolster response rate.

Conclusions

By creating the DT-BCTQ, we reduced the amount of questions needed to pose to a patient from 18 to a maximum of six questions, three for each subscore, when administering the BCTQ while maintaining an ICC of 0.94 with the original BCTQ. This DT-BCTQ might reduce patient burden by shortening answer time and may improve patient-perceived

content validity. As such, the DT-BCTQ could increase response rate when used for routine outcome measurement. This might especially be beneficial in clinics where patients are asked to fill in multiple questionnaires at frequent timepoints. Future research into the DT-BCTQ could focus on multiple aspects, such as the reliability and responsiveness of the DT-BCTQ in comparison with the original BCTQ, clinical implementation of the DT-BCTQ and the experiences of patients with the electronic DT-BCTQ. In this way, the collection of data in clinical practice and CTS research through the BCTQ can be optimized to improve response rates and reduce response burden for patients in the future.

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SUPPLEMENTARY FIGURES

Supplementary Figure 1
Only available at:
https://www.archives-pmr.org/article/S0003-9993(19)30390-9/fulltext#supplementaryMaterial

Supplementary Figure 2
Only available at:
https://www.archives-pmr.org/article/S0003-9993(19)30390-9/fulltext#supplementaryMaterial

PART 2

FACTORS INFLUENCING TREATMENT OUTCOME AFTER SURGICAL TREATMENT OF PRIMARY CARPAL TUNNEL SYNDROME

3 | Predicting Clinical Outcome After Surgical Treatment in Patients With Carpal Tunnel Syndrome

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ABSTRACT

Purpose

Carpal tunnel release (CTR) is typically offered to patients with electrophysiological abnormalities when night splints no longer prevent waking with numbness, and preferably before there is any static numbness, weakness, or atrophy. The ability to predict the amount of symptom relief after CTR could be beneficial for managing patient expectations and therefore improve treatment satisfaction. Therefore, the aim of this study is to identify predictors for symptom relief after CTR and to determine their contribution in symptom relief at six months postoperatively.

Methods

1049 patients that requested CTR between 2011 and 2015 at one of eleven Xpert Clinics in the Netherlands were asked to complete online questionnaires at intake, three months and six months postoperatively. Patient demographics, comorbidities and baseline scores were considered potential predictors for the amount of symptom relief on the Boston Carpal Tunnel Questionnaire(BCTQ)-score, which was the primary outcome measure.

Results

A low score on the BCTQ at intake, a co-diagnosis of a trigger finger, ulnar nerve neuropathy, trapeziometacarpal joint arthrosis, or midcarpal instability were associated with a smaller improvement in the BCTQ domains after a CTR at six months postoperatively and accounted for 35-42% of the variance on the BCTQ domains in our multivariable regression models.

Conclusions

Results of our study can be used to pre-operatively manage patient expectation on symptom relief from surgical treatment. Since only a relatively small (approximately 40%) of the variance can be explained using the present variables, we suggest that future research on predictive factors for symptom relief after CTR focus on other factors, including non-physical factors such as mental health, pre-operative expectations and disease awareness.

Level of evidence: Level II, prognostic

INTRODUCTION

It has already been shown that surgical treatment for carpal tunnel syndrome (CTS) is generally more effective than non-operative treatment (such as splinting or corticosteroid injections) in terms of recurrence rate, improvement of symptoms and hand hand function[1,2]. Although the main goal of CTR is to prevent further progression of disease, a substantial proportion of patients maintain symptoms postoperatively[3,4]. While clinical trials can establish whether a treatment is effective on average, further research is needed to improve the predictability of outcomes after surgical treatment for CTS in individual patients.

The ability to predict symptom relief after CTR is desirable as it could manage patient expectation of the treatment and therefore improve self-reported postoperative well-being[5,6]. Because patients present with different levels of median nerve compression[7], it is presently difficult to predict the outcome after CTR for individual patients with CTS.

Therefore, the aim of this study was to identify those factors that can predict the amount of symptom relief after surgical treatment and to determine the contribution of these factors in predicting the amount of symptom relief for individual patients with CTS. By identifying these predictive factors, our goal is to create a risk model to quantify the amount of symptom relief when treated surgically for CTS.

MATERIALS AND METHODS

Study population

All patients with CTS who were offered surgical treatment between November 2011 and November 2015 in a hand clinic (Xpert Clinic, the Netherlands) were asked to complete online questionnaires in our web-based outcome registration system at intake, three months and six months after surgery. Xpert Clinic is a group of specialized clinics in 11 locations throughout the Netherlands with, at the time of the study, twelve European Board certified (FESSH) hand surgeons performing procedures.

We included patients who received a CTR and had filled-in the Boston Carpal Tunnel Questionnaire[8] (BCTQ) as part of routine clinical care at intake and six months postoperatively. We excluded patients with previous surgical treatment for CTS on the ipsilateral hand. In patients who underwent bilateral CTR, only the first treated hand was included. For this study, we decided not to exclude patients with specific comorbidities or concomitant surgeries because these factors could be potential predictors of symptom relief after CTR. We adhered to the STROBE-guidelines. Furthermore, the study was approved by the local institutional review board and written informed consent was obtained from all patients.

Treatment

All patients underwent an open CTR. Subsequently, all patients received standard postoperative care which consisted of three to five days of bandages and a sling around the operated hand. After this, standardized hand therapy, consisting of nerve and tendon gliding exercises, was started by a hand therapist. Patients were seen at our outpatient clinic within fourteen days postoperatively to monitor progress and to remove sutures.

MEASUREMENTS

Baseline characteristics

We collected sociodemographic data preoperatively from all patients including age, sex, hand dominance, duration of symptoms, BMI, occupation, smoking and alcohol usage. Patients were diagnosed with CTS by a physician based on a combination of symptoms physical examination and electrodiagnostic testing. In addition, information on the presence of comorbidities was retrieved from the medical record. Comorbidities were diagnosed by a physician based on the medical history, physical examination, radiographic imaging or electrodiagnostic testing. As a rule of thumb, we defined that comorbidities and concomitant procedures needed a minimum of ten cases to be included in the analyses. Moreover, the comorbidities ulnocarpal impingement, scaphoid nonunion collapse (SNAC) wrist, pisotriquetral arthrosis, distal radioulnar arthrosis and scapholunate dissociation were grouped under the variable 'midcarpal instability'. Cubital tunnel syndrome, Guyon's canal syndrome and unspecified ulnar nerve neuropathy were also grouped under a separate 'ulnar nerve neuropathy' variable.

Primary outcome measurement: Boston Carpal Tunnel Questionnaire

To assess the symptom intensity of CTS, patients filled out the BCTQ (Dutch Language Version[9], BCTQ; 1= no complaints, 5= maximum complaints possible) at baseline, 3 months and 6 months postoperatively. The BCTQ covers two domains; the symptom severity scale (SSS) and the functional status scale (FSS), including eleven and eight items respectively.

Complications

Complications were registered during a six months' period after surgery. These included infections treated with antibiotics, wound dehiscence, iatrogenic median nerve injury and postoperative bleeding.

Statistical analysis

A proportion of the data from the included patients had missing values due to non-response. At baseline, there was a proportion of non-response for the following variables:

BMI (33% missing), duration of symptoms (18% missing), smoking status (33% missing) and alcohol intake (33% missing). Non-response for all other baseline characteristics was 0-3%. Regarding the outcome measurements, there was a non-response of 0%, 8% and 0% for the BCTQ at baseline, 3 months and 6 months, respectively. Because information on the presence of comorbidities and concomitant surgery was retrieved from the medical record for every patient, we had no missing data for these variables.

Because of this proportion of missing values and to check for selection bias in our inclusion criteria, a non-responder analysis for baseline variables was performed (Supplementary Table 1). This analysis was done by conducting Analyses of variance (ANOVA), Chi-square statistics and unpaired T-tests. After Bonferroni correction for multiple testing, we concluded that the missing data was independent of both observable and unobservable variables and could therefore be classified as missing completely at random (MCAR)[10]. Therefore, Multiple Imputation (MI)[11] was used to impute the missing values at baseline and follow-up ten times. The collected data was used as auxiliary variables in our imputation model. Auxiliary variables are variables that are not imputed during the imputation progress, but are used to impute the missing values.

Bivariable analyses were done to identify potential predictive baseline factors for clinical outcome, defined as the difference between baseline and six months postoperative on the SSS-score, the FSS-score and the total BCTQ-score. From these bivariable analyses, all associated variables with a significance of $p < 0.20$ were considered for a backwards multivariable regression analysis. Subsequently, variables with a pooled significance level of <0.05 were used in the final multivariable models.

Because the convergent pattern of the postoperative courses of the different subgroups of patients presented in Figure 1 might be partly explained by regression to the mean, a correction for regression to the mean was done to adjust the postoperative scores of the SSS, FSS and the BCTQ-total by using the method suggested by Kelly et al[12].

RESULTS

Study sample and baseline characteristics

Between November 2011 and November 2015, 2748 patients underwent a primary CTR. After exclusions, the cohort consisted of 1049 patients (Figure 2). Baseline characteristics of the included patients can be found in Table 1.

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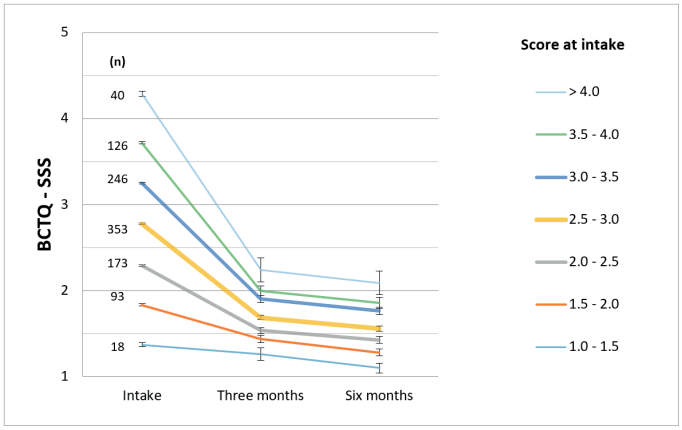

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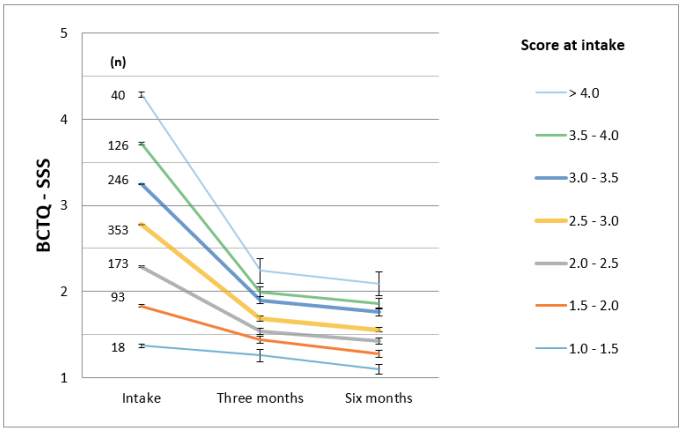

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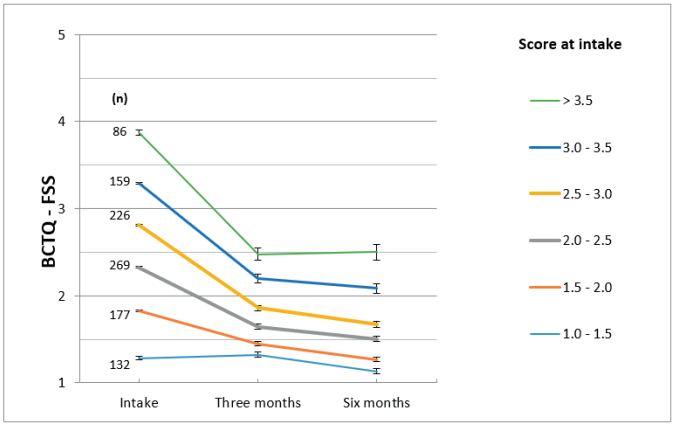

Figure 1. Postoperative course of the BCTQ-scores of subgroups of patients grouped on their score at intake, corrected for regression to the mean. The error bars represent the standard error of the mean.

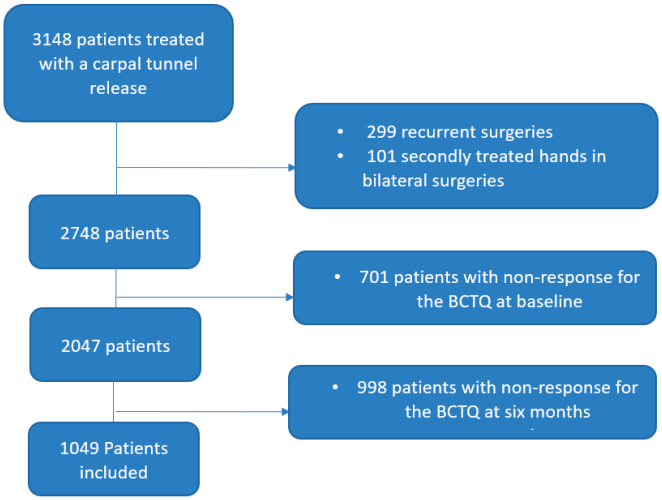

Figure 2. Study flowchart

Surgical outcome

Figure 3 shows a significant mean improvement on all primary and secondary outcomes at six months postoperatively and shows the distributions of these outcomes at intake and six months postoperatively. After six months, 985 patients (93.8%) showed improvement on the BCTQ-total score with a mean improvement of 1.15 points (±0.63). However, 64 patients showed a deterioration on the BCTQ-total score at six months with a mean increase of 0.31 (±0.26). Furthermore, there were 21 complications in 20 patients, consisting of 14 infections and 6 wound dehiscences. One patient had an infection and a wound dehiscence. All 20 patients with a complication did not show deterioration on the BCTQ-total score at six months postoperative.

Predictive factors

Several potential predictive factors were identified from our bivariable analyses (Table 2). Subsequently, these potential predictive factors were used in creating our multivariable models (Table 3). The multivariable models could explain 42%, 38% and 35% of the variance in the model for the change score of the BCTQ-SSS, BCTQ-FSS and the BCTQ-total score at six months respectively. Generally, a more severe score at intake was predictive for a greater improvement on the score at six months for the BCTQ-SSS score, while the presence of trapeziometacarpal joint arthrosis, a trigger finger, ulnar nerve neuropathy on the ipsilateral hand and a high BCTQ-FSS score at intake are predictive for a smaller improvement on the BCTQ-SSS score at six months postoperatively. Likewise, a more severe score at intake and a more physical demanding job was predictive for greater improvement at six months on the BCTQ-FSS score, while the presence of trapeziometacarpal joint

Table 1. Baseline characteristics of the study population (n=1049).

Baseline Characteristics		Study population (n=1049)
Categorical Variables		***(%)***
Sex	**Female**	72
Operated hand	**Right**	61
Smoking		48
Alcohol usage		58
Comorbidities	**Trigger finger**	15
	Trapeziometacarpal joint arthrosis	7
	Diabetes	6
	History of wrist trauma	3
	De Quervain tenosynovitis	3
	Dupuytren's disease	2
	Rheumatic diseases	2
	Guyon's canal syndrome	1
	Cubital tunnel syndrome	2
	Unspecified ulnar nerve neuropathy	1
	Radial tunnel syndrome	1
	Midcarpal instability	1
Concomitant procedures	**Trigger finger release**	10
	Cubital tunnel release	2
	De Quervain release	*1*
	Guyon's tunnel release	*1*
Workload	**No work**	37
	Light physical work	24
	Moderate physical work	24
	Heavy physical work	15
Dominance	**Left**	8
	Right	89
	Co-dominant	3
Continuous Variables		***Mean±SD***
Age (years)		53.9 ± 12.1
BMI (kg/m^2)		27.6 + 5.0
BCTQ (1-5)	**Symptom severity scale***	2.87 ± 0.6
	Functional severity scale*	2.48 ± 0.8
	Total*	2.68 ± 0.6
Duration of complaints in months		34.9 ± 61.3

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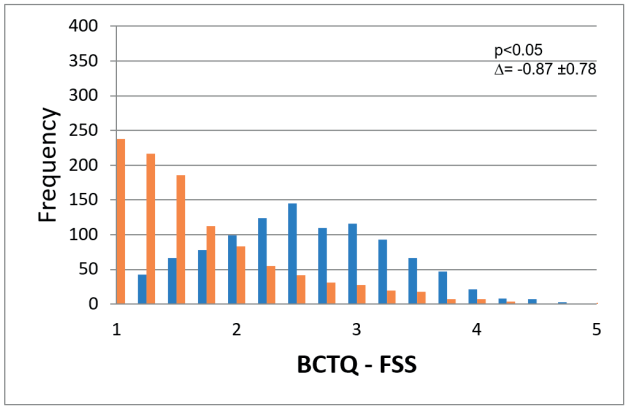

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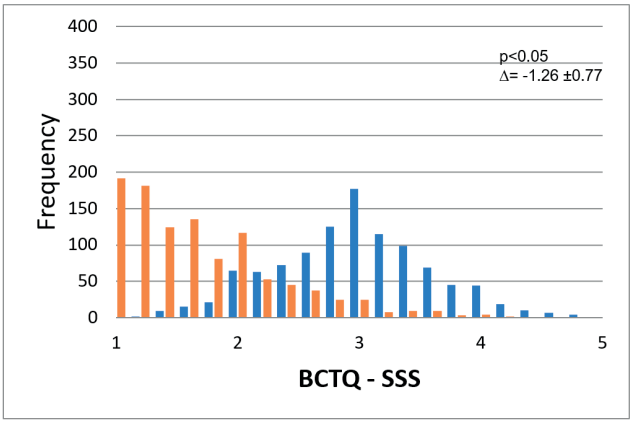

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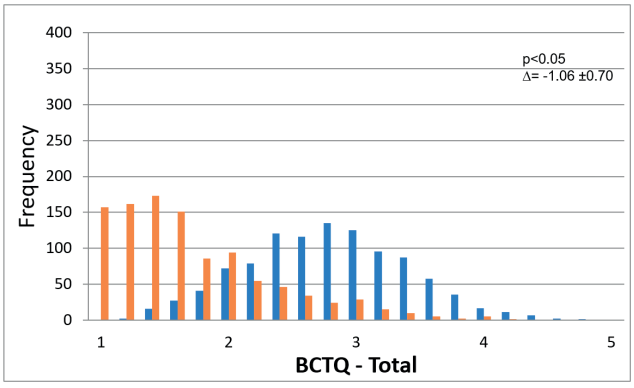

Figure 3. Pre- and postoperative distributions of the BCTQ-scores within the study population at intake and six months postoperative, with the y-axis representing the frequency of the different scores situating on the x-axis. Values in the right upper corner represent T-test p-values and the delta's for the mean differences between the intake and six months postoperative score with the corresponding standard deviation.

Table 2. Bivariable analyses with correlation coefficients representing the relation between baseline variables and surgical effect on the BCTQ-domains.

Baseline Variables			Six months after surgery		
			Δ SSS-score	Δ FSS-score	Δ Total BCTQ -score
Sex		***Female***	0.065*	0.106**	0.094**
Age				0.117**	0.085**
Dominance operated hand		***Yes/No***			-0.058†
Duration of complaints in months			0.075*	0.046†	0.066*
Workload		***Unemployed (reference)***	-0.043†	-0.062†	
		Light physical labor			
		Moderate physical labor			
		Severe physical labor			
BMI					
Smoking		***Yes/No***	-0.082*	-0.093*	
Alcohol usage		***Yes/No***	0.062†	0.060†	0.067†
Comorbidities	**Trigger finger**	***Yes/No***	0.098**	0.044†	0.078*
	Trapeziometacarpal joint arthrosis	***Yes/No***	0,069*	0.070*	0.076*
	Diabetes	***Yes/No***			
	History of wrist trauma	***Yes/No***	0.075*		0.048†
	De Quervain tenosynovitis	***Yes/No***			
	Dupuytren's contracture	***Yes/No***			
	Rheumatoid arthritis	***Yes/No***	0.045†		
	Radial tunnel syndrome	***Yes/No***			
	Midcarpal instability	***Yes/No***		0.042†	
Ulnar nerve neuropathy		***Yes/No***	-0.041†		
	Cubital Tunnel syndrome	***Yes/No***			
	Guyon's canal syndrome	***Yes/No***			
Concomitant procedures	**Trigger finger release**	***Yes/No***	0.062*	0.042†	0.057†
	Cubital Tunnel release	***Yes/No***			
	De Quervain release	***Yes/No***			
	Guyon's tunnel release	***Yes/No***			
BCTQ	***Total***		-0.519**	-0.554**	-0.583**
	SSS		-0.634**	-0.374**	-0.553**
	FSS		-0.302**	-0.605**	-0.500**

***Association found to be significant at a p-level <0.05.**
****Association found to be significant at a p-level <0.01.**
† Association eligible for multivariable analysis at p-level <0.20.
Empty cells indicate a nonsignificant correlation at p=level >0.20

Table 3. Multivariable regression analysis with beta-coefficients representing the relation between baseline variables and the surgical effect on the BCTQ-domains.

Baseline Variables			Six months after surgery		
			Δ SSS-score β (SE)	Δ FSS-score β (SE)	Δ Total BCTQ – score β (SE)
R^2 (% explained variance) for the complete model			**42%**	**38%**	**35%**
Constant			0.834 ** (0.084)	0.750** (0.070)	0.756** (0.084)
Sex		***Female***			
Age					
Dominance operated hand		***Yes/No***			
Duration of complaints in months					
Workload		***Unemployed (reference)***			
		Light physical labor		-0.057** (0.018)	
		Moderate physical labor			
		Severe physical labor			
BMI					
Smoking		***Yes/No***			
Alcohol usage		***Yes/No***			
Comorbidities	**Trigger finger**	***Yes/No***	0.155** (0.050)	0.111* (0.053)	0.133** (0.049)
	Trapeziometacarpal joint arthrosis	***Yes/No***	0.151* (0.071)	0.174* (0.075)	0.163* (0.069)
	Diabetes	***Yes/No***			
	History of wrist trauma	***Yes/No***			
	De Quervain tenosynovitis	***Yes/No***			
	Dupuytren's disease	***Yes/No***			
	Rheumatoid arthritis	***Yes/No***			
	Radial tunnel syndrome	***Yes/No***			
	Midcarpal instability	***Yes/No***		0.552* (0.235)	
Ulnar nerve neuropathy		***Yes/No***	0.182* (0.085)		
	Guyon's canal syndrome	***Yes/No***			
	Cubital tunnel syndrome	***Yes/No***			
Concomitant procedures	**Trigger finger release**	***Yes/No***			
	Cubital tunnel release	***Yes/No***			
	De Quervain release	***Yes/No***			
	Guyon's tunnel release	***Yes/No***			

Table 3. Multivariable regression analysis with beta-coefficients representing the relation between baseline variables and the surgical effect on the BCTQ-domains. (continued)

Baseline Variables		Six months after surgery		
		Δ SSS-score β (SE)	Δ FSS-score β (SE)	Δ Total BCTQ – score β (SE)
BCTQ	*Total*			
	SSS	-0.864** (0.036)		-0.432** (0.035)
	FSS	0.137** (0.031)	-0.636** (0.025)	-0.247** (0.030)

***Association found to be significant at a p-level <0.05.**
****Association found to be significant at a p-level <0.01.**
Empty cells indicate a nonsignificant correlation at p-level >0.05

arthrosis, a trigger finger and midcarpal instability of the ipsilateral hand are predictive for a smaller improvement on the BCTQ-FSS score at six months postoperatively. For the BCTQ-total score at six months, a more severe score at intake for the BCTQ-SSS and the BCTQ-FSS are predictive for a greater improvement, while the presence of a trigger finger or trapeziometacarpal joint arthrosis is predictive for a smaller improvement compared to the score at intake.

Figure 1 further illustrates that the clinical severity of CTS at intake is the most important factor in estimating the effect of surgical treatment. This figure shows the effect of surgery on the BCTQ-scores after three and six months for subgroups of patients defined by their score at intake, corrected for regression to the mean. This figure also indicates that patients with severe CTS symptoms at baseline have approximately the same level of residual symptoms at six months postoperatively as those with less severe CTS symptoms at baseline.

DISCUSSION

In this study, we showed that clinical severity of carpal tunnel syndrome (CTS) at intake is the most important factor in estimating the symptom relief after surgical treatment, as patients with more severe CTS at intake experienced greater effect of carpal tunnel release (CTR) on the BCTQ. Although the amount of symptom relief after CTR is higher for patients with more severe CTS, these patients might also have more residual symptoms. However, Figure 1 shows that the amount of residual symptoms at six months postoperatively of patients with severe CTS symptoms at baseline is close to the amount of residual symptoms at six months postoperatively of patients with less severe CTS symptoms at baseline. By

using multivariable models, we could explain 37-41% of the variation in treatment effect on the Boston Carpal Tunnel Questionnaire (BCTQ). This means that the majority of the variation between the outcomes between different patients (≈60%) cannot be explained by the variables included in the present study. Therefore, this study might not give a precise prediction on the amount of symptom relief, but might give an estimation on what a patient could expect in terms of symptom relief.

This study confirms that surgical treatment of CTS is, on average, effective for improving function and symptom intensity[1,13,14]. However, our study also shows (Figures 1 and 3) that mean improvement might not be a relevant measure for individual patients because of the wide variation in symptom relief between individual patients. Therefore, clinical severity of CTS at intake and the presence of comorbidities, especially the presence of trapeziometacarpal joint arthrosis, midcarpal instability, ulnar nerve neuropathy or a trigger finger should be considered when estimating the individual symptom relief after surgical treatment for CTS. Results of our study can be used as a tool to identify pre-operatively the amount of symptom relief a patient can expect from surgical treatment at six months post-operatively. This information could be of importance in adjusting the individual patient expectations of surgical treatment for CTS[15].

Although we tested 28 variables, only a few variables were found to have predictive value for the effect of surgery on the BCTQ-score. At present, few and relatively small studies have performed similar analyses. Conzen et al. found similar results in the way that the amount of improvement after CTR is largely independent of socio-demographic characteristics[16]. Moreover, our study is in line with Burke et al. who found that patients with more severe symptoms, as determined by patient self-assessment at intake, have a greater improvement in the symptom severity and hand function postoperative[17].

The lack of predictive value of most our evaluated baseline characteristics, as well as the approximately 60% unexplained variance, may indicate that other variables play a role that were not examined. For example, multiple studies have shown that mental health plays an important role when evaluating treatment effect on self-reported upper extremity health[18,19]. In addition, pre-operative expectations influence postoperative patient reported outcomes and could be of importance when predicting individual success of CTR[20]. Therefore, future research should focus on the role of non-physical factors in predicting treatment outcome after carpal tunnel release.

Several limitations of our study should be considered. First, an important limitation is that the presence of comorbidities might not be predictive for the response to CTR because patients with these comorbidities might also have been responding to the BCTQ for their persistent symptoms related to these comorbidities. This could mean that the BCTQ is an insensitive outcome measure as it does not only reflect median nerve dysfunction. In addition, some comorbidities present within our study sample could have been missed by the physician and were therefore not diagnosed. Second, because the completion of our

questionnaires in daily clinical practice was on voluntary basis, we have a high amount of missing data. Because of the amount of missing data we could not conduct a complete case analysis and only identify 40% of our CTS patients as eligible for inclusion. Because of this missing of data, our study sample might not be a valid representation of our CTS patient population and imputing the data could then give misleading results[21]. However, a non-responder analysis indicated that the missing data pattern was at random and that there were no differences between included and excluded patients at baseline. Therefore we could safely impute the data by using multiple imputation[22] We therefore assumed that our study sample is a valid representation of our CTS patient population. By doing so, we could obtain information on over 1000 patients, which, in combination with the detailed information about the individual patients and their outcome, is unique in this field of research. Third, our study lacked information on nerve conduction study results. At Xpert Clinic, all patients receive electrodiagnostic testing as a part of routine practice for carpal tunnel syndrome. However, unfortunately, the outcomes of electrodiagnostic testing were not reported in a consistent and standardized format. Therefore, this information was of insufficient quality to be included in our analyses. Although the predictive value of electrodiagnostic measurements in predicting surgical outcome after CTR is heavily debated in literature and does not seem to be of additional value in predicting surgical outcome[23-25], additional information on median nerve conduction might have improved the explained variance of our model. Fourth, information on chronic pain and centralized pain conditions such as fibromyalgia and complex regional pain syndrome was also not accessible in a consistent and accessible format. Fifth, CTR procedures in our cohort were performed by specialists highly trained in hand surgery and therefore may lead to a larger effect on the BCTQ then procedures performed by other medical specialties. However, because CTR can be seen as a relative simple procedure, this is not likely to influence the generalizability of the results of our study. Sixth, the BCTQ might not be able to distinguish between symptoms that are permanent, such as static numbness, from those that are correctable, such as intermittent numbness. Also, caution should be advised for patients who have asymptomatic median nerve entrapment. In addition, although Figure 1 is corrected for regression to the mean, the postoperative course of the BCTQ-scores of subgroups of patients might be influenced by a ceiling- and bottom effect of the BCTQ. Lastly, it has been estimated that around 58% of recurrent surgeries done because of non-response to CTR are done due to incomplete release of the carpal ligament[26] and 23% because of scarring in the postoperative period[27]. Unfortunately, our study is not able to discriminate between the different causes of non-response to CTR and is only able to give a prediction for the amount of symptom relief patients could expect.

In conclusion, this study contributes to a better understanding of the capabilities of surgical treatment in relieving symptoms and improving function for different subgroups of patients as well as management of expectations. However, still a significant proportion of

the variability in symptom relief remains unexplained. We suggest that future research on predictive factors focus more on non-physical factors such as mental health, pre-operative expectations and disease awareness. This way, patients at risk for a low postoperative satisfaction can be identified and targeted for elaborate expectation management.

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4 | Hand Surgeons Performing More Open Carpal Tunnel Releases Do Not Show Better Patient Outcomes

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ABSTRACT

Background

Although previous studies have shown that more experienced surgeons have better patient outcomes following a variety of procedures, in hand surgery and carpal tunnel release in particular, this relation remains unknown. We assessed whether there is an association between surgeon volume and patient outcomes following open carpal tunnel release.

Methods

Patients who underwent carpal tunnel release between 2011 and 2015 at outpatient hand surgery clinics in the Netherlands were included. Surgeon annual volume was defined as the average number of carpal tunnel releases performed per year per participating surgeon over the study period. Primary outcome measures were the Symptom Severity Scale (SSS) and Functional Status Scale (FSS) of the Boston Carpal Tunnel Questionnaire 6 months postoperatively. Multilevel random intercept linear regression analyses were performed to assess whether there was an association between surgeon annual volume and outcome measures, with adjustment for patient characteristics, concomitant procedures and intake score on the Boston Carpal Tunnel Questionnaire.

Results

A total of 1345 patients were included, operated on by 17 surgeons. Median annual surgeon volume was 75 (interquartile range, 50 to 149). Only 0.5% to 0.6% of the total variance in patient outcome on the Boston Carpal Tunnel Questionnaire could be explained by random differences between surgeons. We did not find an association between annual surgeon volume and outcome measures 6 months postoperatively (SSS: β = .000, 95% confidence interval [CI] -.001 - .001, FSS: β =.000, 95% CI -.001 - .001).

Conclusions

In our sample of highly specialized hand surgeons operating in high-volume centers, we found no differences in outcome between high- and low-volume surgeons.

INTRODUCTION

Previous studies have shown that more experienced surgeons have better patient outcomes following a variety of surgical procedures, including gastrointestinal, cardiac, lung, and vascular operations[1-4]. In addition, such relationships have also been found in surgery of the musculoskeletal system[5-7]. Because it can be challenging to quantify a surgeon's cumulative surgical experience for a specific procedure and cumulative experience can be deceptive, annual operative volume is often used to assess the relationship between surgeon volume and patient outcome[1-4].

Carpal tunnel release is one of the most common surgical procedures and the most frequently performed surgery of the hand and wrist, with estimates of 400.000 to 600.000 carpal tunnel releases performed annually in the United States[8,9]. Nevertheless, in hand surgery in general, and in carpal tunnel release in particular, it remains unknown whether there are outcome benefits to repetition for individual surgeons.

There are various reasons why experience might be beneficial in the context of carpal tunnel release. For example, a higher volume surgeon might be better prepared to handle anatomical variations, extensive fibrosis, or other challenging situations. In addition, incomplete transection of the transverse carpal ligament is a relatively common reason for unrelieved symptoms following carpal tunnel release[10,11], which might be less likely to occur in more experienced surgeons.

Conversely, despite the specific challenges of carpal tunnel release, it has been suggested that trained nurse practitioners might be able to perform carpal tunnel release with the same results on patient outcome as achieved by surgeons[12,13]. A reported argument for having a nurse practitioner operate is reduction in waiting time for carpal tunnel release[12,13]. This suggests that operator's education is not considered a predictor for outcome after carpal tunnel release.

A recent study assessed the effects of hand fellowship training on rates of complications for both endoscopic and open carpal tunnel release[14]. Neither operative technique nor type of fellowship training (hand fellowship training versus non-hand fellowship training) had a statistically significant impact on overall complication rates, suggesting that for carpal tunnel release specifically there is no association between surgeon training and complication rate. However, these results were not adjusted for potential confounding factors or for baseline measurements. Fellows were possibly less likely to treat complicated cases (e.g., patients with comorbidities or more severe symptoms) compared to more-senior hand surgeons. Furthermore, it has not been assessed whether, within the surgeon population, there is an association between surgeon experience and patient outcome.

Therefore, the aim of this study was to assess whether there is an association between annual surgeon volume and patient outcomes at 6 months postoperatively after open carpal tunnel release.

METHODS

Data collection

All patients with carpal tunnel syndrome (CTS) who underwent carpal tunnel release between 2011 and 2015 at one of the 11 specialized outpatient hand surgery clinics (Xpert Clinic) in the Netherlands were eligible for the study. As part of routine clinical care, patients were included in a large multicenter web-based database, which contains patient-rated outcome measures. All patients signed informed consent and the study was approved by our local ethics committee. Patients who underwent a primary carpal tunnel release and had at least a baseline measurement and one follow-up measurement on the Boston Carpal Tunnel Questionnaire (BCTQ) were included in the study. Patients where an operative report was not available or the surgeon could not be identified were excluded. In addition, patients operated by a surgeon who performed carpal tunnel releases for less than 1 year in our cohort were also excluded.

Covariates of interest

The following study data were abstracted from the database, because they are known prognostic factors for clinical outcome following carpal tunnel release identified based on literature review[15-20]: age, sex, smoking status, alcohol use, and comorbidities (i.e., rheumatoid arthritis, diabetes mellitus, peripheral neuropathy, cervical radiculopathy, trigger fingers, tendinitis, radiocarpal arthritis, carpometacarpal joint arthritis, scaphotrapezotrapezoidal joint arthritis, history of trauma of the wrist, Dupuytren's disease, cubital tunnel syndrome, ulnocarpal impingement, radial tunnel syndrome and Wartenberg syndrome). For the analysis, cubital tunnel syndrome, radial tunnel syndrome, Wartenberg's syndrome and pronator syndrome were grouped under "other nerve compressions". In addition, a group "other comorbidities" was defined, including the following comorbidities: scaphotrapezotrapezoidal arthritis, radiocarpal arthritis, peripheral neuropathy, cervical radiculopathy, and ulnocarpal impingement. Concomitant procedures (i.e., procedures carried out at the same time as the carpal tunnel releases) were scored as well.

Outcome measures

Our primary outcome measure was the BCTQ score at 6 months postoperatively. The scores at intake were also abstracted, to be able to adjust for score at intake. In addition, to illustrate the course of the outcomes on BCTQ, measurements at 6 weeks and 3 months postoperatively were collected as well. Two domains of the BCTQ were assessed: the Symptom Severity Scale (SSS) and the Functional Status Scale (FSS). The SSS and FSS consist of 11 and 8 items, respectively. All items of both scales have five response categories ranging from 1 to 5, and higher score represents worse symptoms/lower level of function. Responses to items were averaged to create an overall score for each domain[21].

The secondary outcome measure was overall pain assessed using the Visual Analog Scale (VAS), ranging from 0 to 100, 6 months postoperatively. Higher score represents greater pain intensity. The VAS was performed at intake and 6 weeks, 3 months and, 6 months postoperatively.

In addition, adverse events were scored, including infections treated with antibiotics, wound dehiscence, postoperative bleeding, and neuroma of the median nerve. We scored only adverse effects directly related to the carpal tunnel release. Information on the presence of adverse events was abstracted from the medical charts (S.E. and M.C.J.).

Main exposure variable: annual surgeon volume

Surgeon volume was defined as all carpal tunnel releases, including reoperations and concomitant interventions, performed by the participating surgeon, divided by the number of years the surgeon performed carpal tunnel releases during the study period. Similar definitions of annual surgeon volume have been described previously [1,7,22]. All procedures were performed by European board-certified hand surgeons or surgeons following a hand fellowship.

Procedure

All patients underwent an open carpal tunnel release. Neither endoscopic procedures nor modifications were performed. In general, the following protocol was used in all treatment centers within the Xpert Clinic group, with only minor variations between surgeons: longitudinal incision was placed through the subcutaneous fat and palmar fascia until Guyon canal. Fibers were revealed in the radial-ward direction and the transverse carpal ligament was divided. The median nerve was separated from the roof of the carpal tunnel in the proximal direction using scissors, where potential transverse fibers could be dissected. Subsequently, the tendons and median nerve were inspected. When hemostasis was obtained, the fat was repositioned and the skin sutured with 4-0 (Ethicon, Inc., Somerville, N.J.). Sterile dressing and compression bandage was applied. All patients received standard postoperative care and hand therapy by a hand therapist consisting of nerve and tendon-gliding exercises.

Statistical analysis

Parametric data were presented as mean and standard deviation (SD) and nonparametric data as median and interquartile range (IQR). We categorized the variable “annual surgeon volume” for presentation purposes, using tertile-derived categories, into three subgroups: low-volume, medium-volume, and high-volume surgeons. Given the number of missing values, a non-responder analysis at six months postoperatively for baseline variables was performed using chi-square statistics and unpaired T-tests. Based on this analysis we concluded that missing data could be classified as “missing completely at random”.

Therefore, we used multiple imputation to impute the missing values[23]. Ten versions of the data set were produced and independently analyzed, each with its own set of imputed values. To give a single mean estimate, the pooled estimates of ten imputed data sets were used as statistical results.

Because of the hierarchical structure of the data (level 1 = patients, level 2 = surgeons), multilevel random intercept linear regression analyses were performed to assess whether there was an association between surgeon annual volume and outcome measurements. First, we ran an intercept-only model to assess whether there was a significant difference in patient outcome across surgeons, regardless of surgeon volume. In addition, we calculated the intraclass correlation coefficient (ICC) to assess the overall variability in patient outcomes between surgeons. An ICC close to zero would suggest no substantial variability between surgeons in patient outcomes. To adjust the estimated effect of surgeon volume for known prognostic factors identified based on literature review, the variables age, sex, smoking status, alcohol use, comorbidities, concomitant procedures and intake score for the respective questionnaire were included in the model as fixed factors. Values of p <0.05 were considered statistically significant. Analyses were performed using IBM SPSS Version 21 (IBM Corp., Armonk, N.Y.).

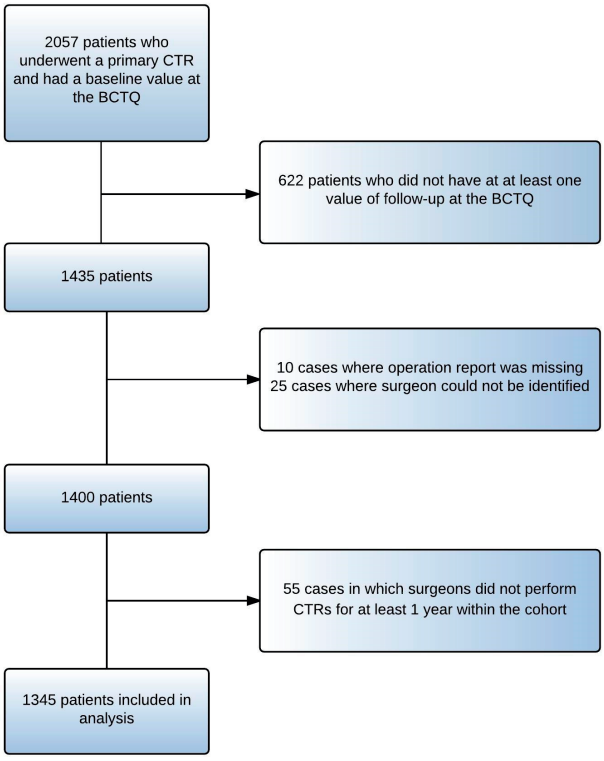


Figure 1. Subject selection flow chart.

RESULTS

A total of 2057 patients who underwent carpal tunnel release within the specified time window were identified. After exclusions, 1345 patients were eligible for this study (Figure 1), operated on by 17 surgeons: 16 hand surgeons and one surgeon in hand fellowship training. The annual surgeon volume ranged from six to 163 procedures per year, with a median (IQR) volume of 75 procedures (50 to 149) (Figure 2). Some of the variables had missing values due to non-response. Regarding the baseline variables, there were missing values for smoking status (35% missing) and alcohol use (35% missing). The proportion of missing data for all other baseline variables ranged from 0 to 1%. Regarding the outcome measures, there were nonresponse rates of 0%, 52%, 13% and 27% for both the SSS and the FSS score at baseline, 6 weeks, 3 months, and 6 months postoperatively, respectively. These were 3%, 9%, 15% and 28% for the VAS score. Because adverse events were reported in only 23 cases (1.6%), we did not use this variable as an outcome measure. Adverse events included wound infection in 18 cases and wound dehiscence in 5 cases. There were a total of 212 concomitant procedures. Table 1 shows the demographic, clinical, and procedural characteristics of the cohort.

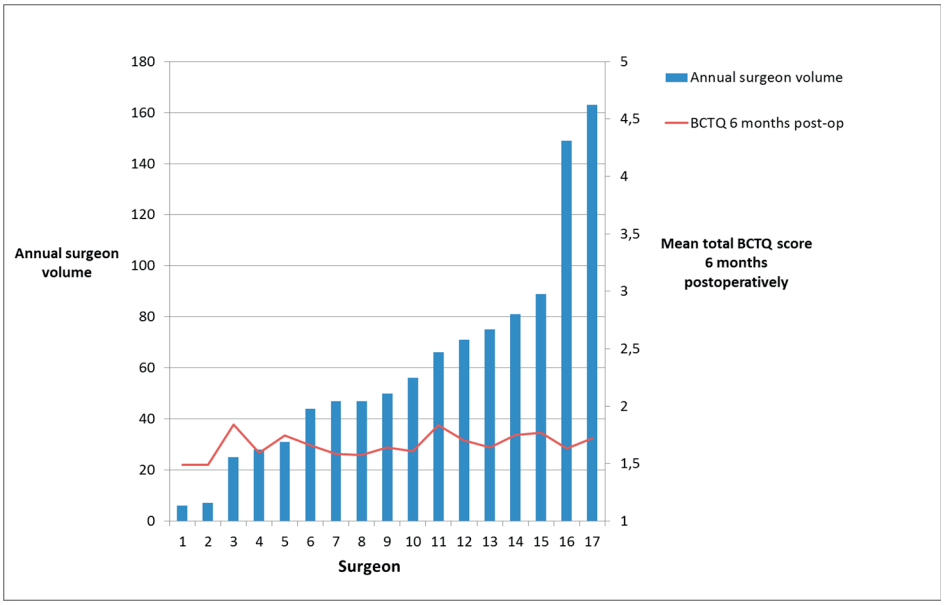


Figure 2. Distribution of number of carpal tunnel releases performed per year (y-axis)) per participating surgeon within the cohort (x-axis).

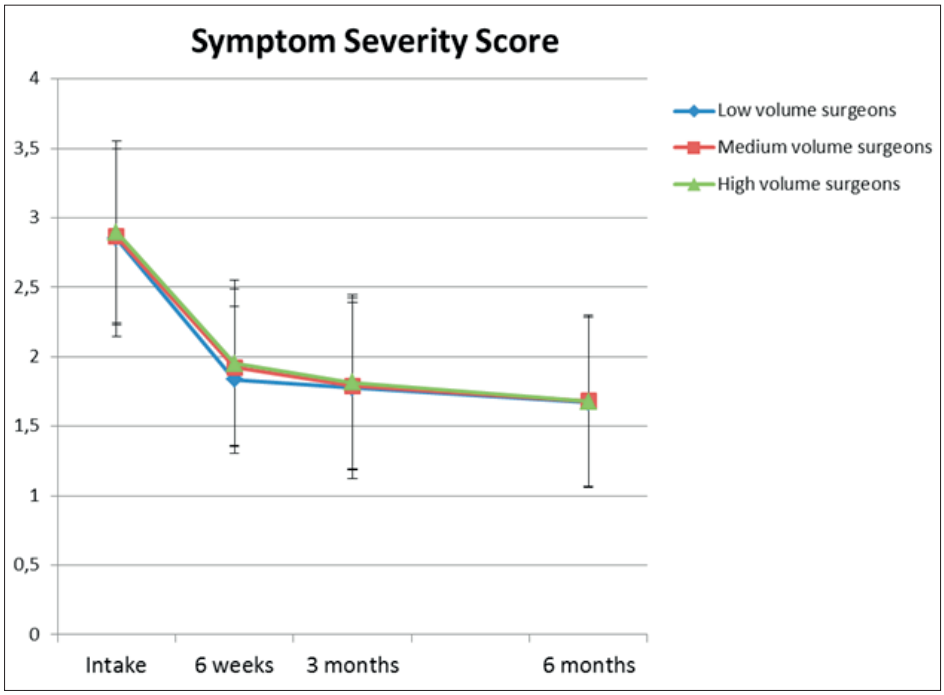
Table 1. Demographic, clinical and procedural characteristics of the CTR cohort.

	Total cohort (N= 1345 patients)
Age, years (SD)	54 (13)
Female (%)	986 (73)
BMI (SD)	27 (5)
Smoking status (smoker: yes) (%)	263 (20)
Alcohol use (drinker: yes) (%)	776 (58)
Comorbidities (%)	
Diabetes Mellitus	68 (5.1)
Rheumatoid Arthritis	19 (1.4)
Dupuytren's disease	30 (2.2)
Trigger fingers	190 (14)
CMC1-arthritis	93 (6.9)
Compression Neuropathy	81 (6.0)
Tendinitis	38 (2.8)
History of wrist trauma	43 (3.2)
'Other'	33 (2.6)
Concomitant procedures (%)	
CTR + Trigger Finger Release	122 (9.1)
CTR + Cubital Tunnel Release	29 (2.2)
CTR + Guyon Release	23 (1.7)
CTR + Radial Tunnel Release	8 (0.6)
CTR + fasciotomy Dupuytren	9 (0.7)
CTR + 'other' procedure	21 (1.6)

CTR= Carpal Tunnel Release

Figures 3 and 4 illustrate the course of the outcome measures, from intake to 6 months postoperatively, grouped by whether the surgeon was a low-, medium- or high-volume surgeon for this procedure. The boundaries for the low-, medium- and high-volume group were 6 to 44, 47 to 71 and 75 to 163 operations annually, and there were 171, 459 and 715 patients in the low-, median- and high-volume group, respectively. The low-, median- and high-volume group included six, six, and five surgeons, respectively.

The intraclass correlation coefficients (SSS, $\rho = 0.005$; FSS, $\rho = 0.006$; VAS, $\rho = 0.002$) indicated that, respectively, only 0.5%, 0.6%, and 0.2% of the patient outcome variance on the SSS, FSS and VAS 6 months postoperatively could be explained by random differences between surgeons. Unadjusted and adjusted models for the association between annual surgeon volume and patient outcome on the BCTQ (SSS and FSS domains) and VAS overall pain indicated no significant association between annual surgeon volume and patient outcome 6 months postoperatively for any of the outcome measures (Table 2). To assess whether the patient outcomes of the surgeon following a fellowship influenced the overall results, we also ran the analysis on the dataset including board-certified hand surgeons only. The results remained unchanged.



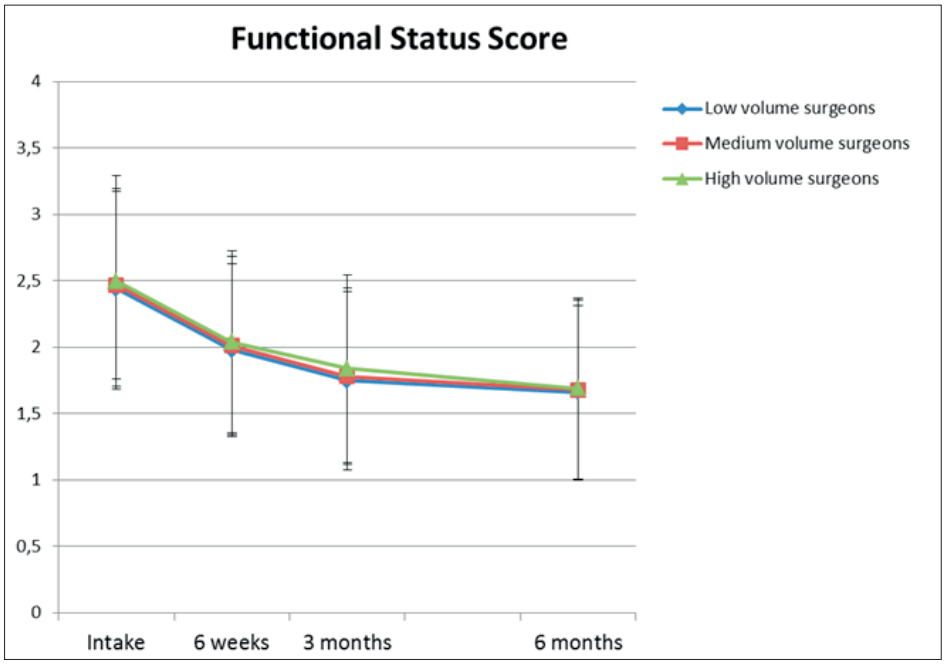


Figure 3. A) Mean Symptom Severity Score (SSS) and B) Mean Functional Status Score (FSS) preoperatively and at 6 weeks, 3 months, and 6 months postoperatively in patients undergoing open carpal tunnel release grouped. Outcomes are divided by whether the surgeon was a: low, medium or high volume surgeon for this procedure. Error bars represent one standard deviation.

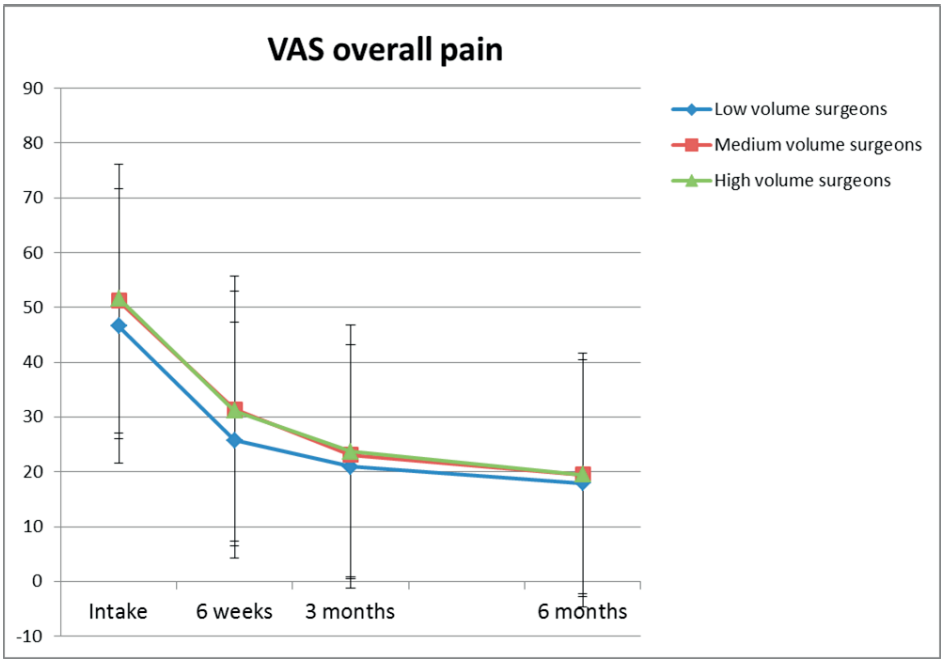


Figure 4. VAS overall pain preoperatively and at 6 weeks, 3 months, and 6 months postoperatively in patients undergoing open carpal tunnel release. Outcomes are divided by whether the surgeon was a: low, medium or high volume surgeon for this procedure. Error bars represent one standard deviation.

Table 2. Uni- and multivariable analysis for association between annual surgeon volume (continuous variable) and the three outcome measurements: Symptom Severity Score (SSS), Functional Status Score (FSS) and Visual Analog Scale (VAS) overall pain at 6 months postoperatively.

Dependent variables	**Unadjusted model†** **β (95%, CI)** for annual surgeon volume effect	**Adjusted model*** **β (95%, CI)** for annual surgeon volume effect
BCTQ: SSS	.000 (-.001 - .001)	-.000 (-.001 - .001)
BCTQ: FSS	.000 (-.001 - .001)	-.000 (-.001 - .001)
VAS: overall pain	.006 (-.025 - .037)	-.002 (-.027 - .023)

CI, confidence interval

†Unadjusted model: univariable analysis for the association between annual surgeon volume and patient outcome.

*Adjusted model: adjusted for score at intake for respective questionnaire, age, sex, smoking status, alcohol use, concomitant procedure, comorbidities: diabetes mellitus, rheumatoid arthritis, CMC1-arthritis, Dupuytren's disease, trigger fingers, tendinitis, history of trauma of the wrist, compression neuropathy, and the group 'other' comorbidity.

DISCUSSION

This study, based on a large cohort and including highly specialized surgeons only, did not show an association between annual surgeon volume and patient outcome after an open carpal tunnel release assessed using the BCTQ and the VAS. In addition, we found that only 0.6% of the variance on the BCTQ 6 months postoperatively could be explained by random differences between surgeons, regardless of surgeon volume.

Previous studies have shown an association between surgeon volume and patient outcome, suggesting that centralization of some types of surgery in a small number of centers is beneficial[2,22]. In hand surgery specifically, it is unknown whether there is an association between surgeon volume and patient outcome. It could be argued that surgeon experience might mainly be beneficial in technical challenging procedures, but data are lacking for both more challenging, more complex procedures as well as for more simple procedures in hand surgery.

The overall improvement in functional status and symptom severity found in our study is in line with the literature[24]. Katz et al. described patient outcomes after an open carpal tunnel release carried out by 26 surgeons in different offices in Maine[24] with symptom severity and functional status 6 months postoperatively similar to our results despite symptom severity and functional status at intake being slightly higher compared to our cohort. Mack et al. reported patient outcomes at 3 months after open carpal tunnel release on 134 patients[25] and found a slightly larger change from baseline compared with our results. The total number of reported adverse events was slightly higher compared with our results, with wound dehiscence in 4% and infection in less than 1% of cases compared with 0.4% and 1.3%, respectively, in our study. Smetana et al. reported a similar incidence of wound dehiscence of 1.2% and median nerve palsy or injury in 0.22% of 28.086 cases of isolated open carpal tunnel release while infection rate was not reported[14].

The main strength of our study is the size of the study population and the detailed outcome assessment, compared with many studies only focusing on symptom or pain reduction[26]. We were able to test our hypothesis on a relatively large database because of the unique registration system on clinical outcomes that Xpert Clinic uses. This leads to very small confidence intervals in the main analysis, where clearly indicating a volume effect are lacking. Several limitations of our study should, however, also be considered. The major limitation of our study is the surgeon cohort in which all the procedures were performed (i.e., the cohort of surgeons are highly specialized and the procedures were carried out in highly specialized centers). In contrast, there was still a wide range (6 to 163) in the number of carpal tunnel releases performed by each of the participating surgeons. In addition, it has been recognized that endoscopic carpal tunnel release has a steep learning curve[27-29]. Considering the complexity of this procedure compared with open carpal tunnel release[30], the learning curve for open carpal tunnel release might flatten out

at a relatively early stage that had already been passed by the surgeons in our cohort. Furthermore, because all the procedures were performed within one group of uniformly organized clinics with a similar patient population, we could not account for a potential hospital volume-outcome relation. Previous studies have shown an association between hospital volume and patient outcome beyond surgeon's experience; the relation between the number of patients undergoing a specific surgery at a specific hospital and their post-surgical outcomes indicate that larger-volume hospitals yield better patient outcomes, despite individual surgeon volume[3,31].

In conclusion, our study shows that specialized hand surgeons have similar patient outcomes following open carpal tunnel release and their annual volume does not influence patient outcome. However, whether our results apply to orthopedic surgeons, neurosurgeons, and plastic surgeons in general and, for example, to residents and nurse practitioners still has to be investigated in further studies.

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5 | Influence of illness perceptions, psychological distress and pain catastrophizing on self-reported symptom severity and functional status in patients with carpal tunnel syndrome

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ABSTRACT

Objective

To examine the influence of illness perceptions, pain catastrophizing and psychological distress on self-reported symptom severity and functional status in patients diagnosed with carpal tunnel syndrome (CTS).

Methods

A total of 674 patients with CTS scheduled for surgery at an outpatient treatment center for hand and wrist conditions (September 2017 to August 2018) completed online questionnaires regarding demographic and psychosocial characteristics and self-reported CTS severity. Self-reported severity of CTS was measured with the functional status scale and the symptom severity scale of the Boston Carpal Tunnel Questionnaire. To measure psychosocial factors, the Patient Health Questionnaire-4, Pain Catastrophizing Scale and the Brief Illness Perception Questionnaire were used. Pearson correlation coefficients were calculated to assess univariable relations. Hierarchical linear regression models were used to examine the relation between psychosocial factors and self-reported severity, and the relative contribution of psychosocial factors to self-reported severity, adjusting for patient characteristics and comorbidities.

Results

Medium-sized correlations (range .32 - .44) with self-reported severity were observed for psychological distress, pain catastrophizing, consequences, identity, concern and emotional representation. Furthermore, these factors (except for concern) were also associated with self-reported severity, when adjusted for baseline characteristics and comorbidities. Hierarchical linear regression models showed that these psychosocial factors explained an additional 20-25% of the variance in self-reported severity of CTS.

Conclusion

This study shows that psychological distress, pain catastrophizing and illness perceptions play an independent role in self-reported severity of CTS. Clinicians should take these psychosocial factors into account when they are consulted by patients with CTS.

INTRODUCTION

With a prevalence of approximately 5%, carpal tunnel syndrome (CTS) is the most common entrapment neuropathy of the upper extremity [1]. Initial treatment of CTS can either be nonoperative (e.g. injection, braces) or surgical, depending on severity and patient preference [2]. Nevertheless, surgical decompression of the median nerve with carpal tunnel release results in better outcomes than nonoperative treatment [3]. Consequently, carpal tunnel release has become the most frequently performed surgical procedure for a hand disorder [4, 5].

The severity of nerve compression can be determined by electrodiagnostic testing, which can be seen as an *objective* measure of CTS severity. The *subjective* severity of CTS (e.g. the effect on daily functioning and the severity of symptoms) is often measured with patient-reported outcome measures. Interestingly, although studies are inconclusive as to whether electrodiagnostic findings are related to patient-reported outcome measures [6-10], a relationship has been found between self-reported CTS severity and psychological factors [6, 7, 11-16]. These findings suggest that psychological factors might play a larger role in how patients experience their symptoms than the electrodiagnostic findings.

Various psychosocial factors have been described in relation to self-reported CTS severity, including somatization [6], self-efficacy [11, 13], neuroticism [17], social deprivation [18], kinesiophobia [19], anxiety, catastrophic thinking and depression; the latter three have been investigated most often and are seemingly the most involved in how patients with CTS rate their symptoms [7, 11, 13-17, 19]. Furthermore, depression and pain catastrophizing are known predictors of postoperative outcome [11, 13] and satisfaction with the outcome of carpal tunnel release [20], thereby demonstrating the importance of psychological factors in patients with CTS.

Until now, no studies on the relation between the effect on daily functioning and the severity of symptoms of CTS, and psychosocial factors have also investigated the relationship with illness perceptions. In the common sense model of illness [21], the way patients perceive their disease is crucial for the assessment and interpretation of symptoms. Illness perceptions are known to be associated with disability in patients with hand osteoarthritis [22], and disease-specific measures of functioning in rheumatoid arthritis [23], psoriasis and COPD [24]. Furthermore, interventions that improve illness perceptions lead to better outcomes [25, 26]. Therefore, investigation of the relation between illness perceptions and the effect on daily functioning and the severity of symptoms of CTS may provide important information for psychosocial interventions to improve the way patients experience their symptoms.

The aim of this study was to examine the relationship between illness perceptions and daily functioning and the severity of symptoms in patients diagnosed with CTS who are scheduled for surgery. We expect that patients with more negative illness perceptions will

report more severe CTS symptoms and worse daily functioning. Furthermore, the relative contribution of illness perceptions, pain catastrophizing and psychological distress to self-reported severity of CTS was analyzed.

METHODS

Study population

Eligible for inclusion were all patients who visited one of the 16 locations of Xpert Clinic, specialized hand and wrist surgery clinics in the Netherlands (between September 2017 and August 2018) and who were diagnosed with CTS and scheduled for a primary carpal tunnel release. Diagnosis was made by one of the European board-certified hand surgeons based on history taking and physical examination, according to the Dutch guideline for CTS [2]. When the diagnosis was inconclusive based on clinical findings, additional electrodiagnostic testing was performed. As part of routine care, patients were asked to fill out online questionnaires in our web-based surgical outcome registration, GemsTracker © (GEneric Medical Survey Tracker), a secure web-based application for distribution of questionnaires and forms during medical research and quality registrations. Patients were excluded when they had undergone one or more prior carpal tunnel releases on the ipsilateral side. Furthermore, if patients were scheduled for a carpal tunnel release on both hands, only the first hand was included. Approval for this study was obtained from the local Institutional Review Board and all patients gave written informed consent.

Measurements

The following demographic characteristics were collected: age, sex, BMI, hand dominance, affected hand, duration of symptoms, workload, smoking, alcohol use and comorbidities. Comorbidities were diagnosed by a physician based on the medical history, physical examination, radiographic imaging or electrodiagnostic testing. Comorbidities were systematically screened on every participant and the following were collected; diabetes mellitus, rheumatic diseases, hypothyroidism, trigger finger, first carpometacarpal (CMC1) osteoarthritis, Dupuytren's disease, De Quervain tenosynovitis, cubital tunnel syndrome, other ulnar nerve compressions, radial tunnel syndrome, pronator teres syndrome, trauma of the hand and wrist prior to the start of CTS symptoms, and instability or osteoarthritis of the wrist. Cubital tunnel syndrome, other ulnar nerve compressions, radial tunnel syndrome and pronator teres syndrome were grouped together under 'other nerve compressions' because, combined, they were present in only 3% of our sample. Other potentially relevant comorbidities present in ≤1% of our sample were not reported.

The following questionnaires were used to assess psychological factors in our sample:

Illness perception questionnaire

The Brief Illness Perception Questionnaire [27], a validated questionnaire based on the original and revised Illness Perception Questionnaire [28, 29], is used to assess the cognitive and emotional representations of illness, which are drivers for how patients cope with their illness and several illness behaviors and outcomes [25]. It consists of 8 items regarding different domains of illness perception rated on an 11-point scale. The domain 'consequences' describes the expected effects and outcome of the disease (0=no effect at all, 10=severely affects my life). How long patients believe the illness will last is described by the 'timeline' domain (0 = a very short time, 10 = forever). The 'control' domain (divided into personal control and treatment control), describes to what extent patients believe that they can recover from or control the illness (0 = absolutely no control, 10 = extreme amount of control). The domain 'identity' describes how a patient views illness and symptoms as a part of the disease (0 = no symptoms at all, 10 = many severe symptoms). To what extent the patient understands his disease is described by 'illness comprehensibility' (0 = don't understand at all, 10 = understand very clearly). Finally, the domain 'concern and emotional representation' describes how patients experience emotional complaints due to the disease (0 = not at all concerned/affected emotionally, 10 = extremely concerned/affected emotionally). Higher scores indicate a more threatening view of the illness for the domains consequences, timeline, identity, concern and emotional representation, and lower scores on the domains illness comprehensibility, personal and treatment control reflect more threatening view of the illness. In line with author instructions, the Dutch version of the B-IPQ [30] was adapted to suit our patient sample by replacing the term "illness" by "hand or wrist illness".

Patient Health Questionnaire

The Patient Health Questionnaire-4 [31] is a validated screening tool for anxiety and depression consisting of the Generalized Anxiety Disorder-2 [32] questionnaire and the Patient Health Questionnaire-2 [33]. For each of the four items, patients have to respond to the question "Over the last 2 weeks, how often have you been bothered by the following problems". Responses are scored as 0-3, where 0 is "not at all" and 3 is "nearly every day", resulting in a maximum score of 12. The total score can be interpreted as a degree of psychological distress [31].

Pain Catastrophizing Scale

The Pain Catastrophizing Scale [34] measures exaggerated maladaptive cognitions or emotions in response to noxious stimuli. It is composed of 13 items which can be answered on a 5-point scale, ranging from 0 ("not at all") to 4 ("all the time"). The total score (range 0- 52) is used to assess pain coping strategies.

Primary outcome measure: Boston Carpal Tunnel Questionnaire

The Boston Carpal Tunnel Questionnaire (BCTQ) [35] is a validated questionnaire specifically for assessing patient-reported severity of CTS in the last two weeks. The BCTQ is comprised of two domains, the Symptom Severity Scale (SSS) which measures the severity of CTS symptoms in the affected hand and consists of 11 items (e.g. "How severe is the hand or wrist pain that you have at night?", 1 = normal, 5 = very serious), and the Functional Status Scale (FSS), which measures function of the affected hand in daily activities and consists of 8 items (e.g. "Bathing and dressing", 1 = no difficulty, 5 = cannot perform the activity at all due to hands and wrists symptoms). Averages ranging between 1 and 5 of the respectively 11 and 8 items are used. The Dutch Language Version [36] was used for the present study.

Statistical analysis

To test our first hypothesis, namely a positive association between illness perceptions and self-reported severity of symptoms and daily functioning of CTS, we calculated Pearson product moment correlation coefficients and their p-values. Correlation coefficients (r) were interpreted using the classification described by Cohen [37], i.e. an r of .10 - .30 was interpreted as a small effect, an r of .30 - .50 as a medium effect, and an $r \geq .50$ was interpreted as a large effect. To test the relative contribution of illness perceptions, psychological distress and pain catastrophizing to self-reported severity of CTS, hierarchical regression analyses were used. By entering sets of variables in a specific sequence, we were able to calculate the added amount of explained variance (R^2) in the FSS and SSS score of each set. First, we included patient characteristics and comorbidities in the analysis. Second, psychological distress and pain catastrophizing were entered, because these factors have already been shown to be related to self-reported severity in CTS [7, 14, 17, 19]. In the final step, the domains of illness perception (i.e. our variables of interest which have not been studied in relation to self-reported severity of CTS before) were added to the model to test whether illness perceptions explained unique variance over and above the variables entered in the previous steps. In addition to the R^2, the unstandardized and standardized beta coefficients were calculated. Furthermore, the adjusted R^2, which accounts for the number of independent variables added in the regression analysis, was calculated. Multicollinearity was checked by calculating the variance inflating factor for each variable in both final models, which assesses how much the variance of an estimated regression coefficient increases when predictors are correlated [38]. Two-sided p-values $\leq .05$ were considered statistically significant. The statistical software package R (version 3.5.1) was used for analysis and processing of the data.

RESULTS

Study sample

Since some patients (n=185) did not respond to all of the questionnaires they were excluded from the analysis. To check for differences between responders and non-responders, we performed a non-responder analysis for patient characteristics (Supplementary Table 1). Baseline characteristics between patients who responded to all questionnaires and those who did not, were compared using Chi-square tests for categorical variables and unpaired T-tests for continuous variables. No significant differences were found between the two groups.

Table 1. Patient characteristics of the study sample (n=674).

			Study sample (n=674)
Categorical Variables			***n (%)***
Sex	**Female**		475 (70)
Operated hand	**Right**		388 (57)
Smoking			123 (18)
Alcohol usage			354 (53)
Comorbidities	**Diabetes mellitus**		47 (7)
	Rheumatic diseases		30 (4)
	Hypothyroidism		32 (5)
	Trigger finger		95 (14)
	CMC1 osteoarthritis		46 (7)
	De Quervain tenosynovitis		11 (2)
	Dupuytren's disease		19 (3)
	Other nerve compressions		23 (3)
	(History of) trauma		28 (4)
	Instability or OA of the wrist		21 (3)
Workload	**No work**		217 (32)
	Light physical work		142 (21)
	Moderate physical work		217 (32)
	Heavy physical work		98 (15)
Hand dominance	**Left**		41 (6)
	Right		641 (91)
	Co-dominant		19 (3)
Continuous Variables			***Mean ± SD***
Age (years)			54.5 ± 13.9
BMI (kg/m^2)			27.6 ± 4.9
BCTQ (1-5)		**Functional severity scale**	2.35 ± 0.8
		Symptom severity scale	2.87 ± 0.6
Duration of complaints in months			22.6 ± 41.5

CMC1 osteoarthritis = first carpometacarpal osteoarthritis; BCTQ=Boston Carpal Tunnel Questionnaire

Subsequently, a total of 674 patients scheduled for carpal tunnel release who completed all questionnaires (preoperatively) were included in this study, i.e. 475 women and 199 men with a mean age of 54.5 years. Table 1 presents patient characteristics and Table 2 the means and standard deviations (SD) of psychological distress, pain catastrophizing and illness perception scores for the study sample.

Table 2. Mean scores of psychological distress, pain catastrophizing and Illness perceptions and their correlations with symptom severity and functional status.

Measure	Mean ± SD	Correlation coefficient	
		FSS	SSS
Psychological distress (0-12)	1.4 ± 2.4	.32***	.25***
Pain catastrophizing (0-52)	13.3 ± 10.9	.35***	.38***
Illness perceptions (0-10)			
Consequence	6.9 ± 2.3	.39***	.40***
Timeline	4.9 ± 2.6	.21***	.07*
Control (personal)†	4.1 ± 2.5	-.04	-.10**
Control (treatment)†	8.5 ± 1.4	.06	.06
Identity	6.4 ± 2.4	.40***	.44***
Concern	5.5 ± 2.8	.35***	.33***
Illness comprehensibility†	8.0 ± 2.2	-.07	-.01
Emotional representation	4.5 ± 3.1	.35***	.38***

* P < .05, ** P < .01, *** P < .001, † higher scores reflect more positive perceptions. SD=standard deviation, SSS=symptom severity scale, FSS=functional status scale

Correlations between BCTQ scores and psychological factors

Correlations between FSS, SSS, and psychological distress, pain catastrophizing and illness perception domains are presented in Table 2. Medium-sized correlation coefficients were observed for most psychological factors and illness perceptions (i.e. psychological distress, pain catastrophizing, consequences, identity, concern and emotional representation). For the other psychosocial factors either small (i.e. timeline, personal control) or non-significant correlations (treatment control, illness comprehensibility) were found.

Contribution of psychological factors to daily functioning and severity of symptoms

The results of the hierarchical linear regression analysis are presented in Table 3A and Table 3B. The explained variance for patient characteristics and comorbidities was 15% and 8% for the FSS and SSS score, respectively. In the second step, psychological distress and pain catastrophizing added 11% and 12% explained variance for the FSS and SSS score, respectively. In the final step the 8 domains of illness perceptions were entered, which added 9% and 13% of explained variance for the FSS and SSS score, respectively.

Table 3A. Hierarchical regression analysis for factors influencing self-reported daily functioning in carpal tunnel syndrome patients, showing estimated effect sizes and additional explained variance per step.

Predictors	Functional status scale (range 1-5)					
	Model 1		Model 2		Model 3	
	B (SE)	β	B (SE)	β	B (SE)	β
Step 1: Patient characteristics and comorbidities						
Age	-.003 (.003)	-.049	-.001 (.003)	-.010	.001 (.002)	.014
Male (reference female)	**-.353 (.072)**	**-.427*****	**-.325 (.067)**	**-.393*****	**-.285 (.064)**	**-.345*****
BMI	**.013 (.006)**	**.079***	**.016 (.006)**	**.098****	**.013 (.006)**	**.080***
Smoking	**.261 (.081)**	**.316****	**.164 (.076)**	**.199***	**.144 (.072)**	**.174***
Alcohol usage	-.089 (.063)	-.108	-.061 (.059)	-.073	-.044 (.056)	-.054
Workload (reference: not working)	/	/	/	/	/	/
Light physical work	-.068 (.092)	-.083	.043 (.086)	.052	.032 (.082)	.039
Moderate physical work	-.005(.085)	-.006	.030 (.079)	.037	.009 (.076)	.011
Heavy physical work	.001(.109)	.002	.040 (.102)	.048	-.008 (.098)	-.010
Duration of symptoms	**.002 (.001)**	**.077***	**.002 (.001)**	**.090****	**.002 (.001)**	**.092****
Diabetes mellitus	**.295 (.123)**	**.356***	**.236 (.115)**	**.286***	.170 (.110)	.205
Rheumatic diseases	**.437 (.148)**	**.528****	**.413 (.138)**	**.500****	**.313 (.133)**	**.379***
Trigger finger	**.294 (.088)**	**.355*****	**.274 (.082)**	**.331*****	**.230 (.079)**	**.279****
CMC1 osteoarthritis	.235 (.121)	.284	.218 (.113)	.264	.176 (.108)	.212
Dupuytren's disease	.256 (.183)	.310	.120 (.171)	.145	.160 (.163)	.193
De Quervain tenosynovitis	.275 (.242)	.332	.329 (.226)	.398	.253 (.214)	.306
Trauma of the hand/wrist	**.303 (.152)**	**.366***	.214 (.142)	.259	**.271 (.135)**	**.328***
Instability and/or osteoarthritis of the wrist	-.196 (.174)	-.236	-.177 (.162)	-.214	-.265 (.155)	-.321.
Hypothyroidism	.031 (.145)	.038	-.065 (.135)	-.079	.006 (.130)	.008
Other nerve compressions	.316 (.167).	.382	.172 (.156)	.208	.266 (.149)	.321.
Step 2: Psychological distress and pain catastrophizing						
Psychological distress			**.052 (.014)**	**.152*****	**.041 (.013)**	**.119****
Pain catastrophizing			**.019 (.003)**	**.247*****	**.009 (.003)**	**.115****
Step 3: Illness perceptions						
Consequences					**.060 (.016)**	**.165*****
Timeline					.014 (.012)	.043
Control (personal)					-.011 (.011)	-.033
Control (treatment)					-.018 (.021)	-.030
Identity					**.059 (.015)**	**.173*****
Concern					.003 (.013)	.009
Illness comprehensibility					-.013 (.013)	-.033
Emotional representation					.008 (.012)	.029
R^2	.152		.264		.351	
Adjusted R^2	.128		.240		.332	

Bold indicates a significant association. * P < .05, ** P < .01, *** P < .001, B = unstandardized beta coefficient, β = standardized beta coefficient (for categorical predictors only the outcome was standardized), SE = standard error

Table 3B. Hierarchical regression analysis for factors influencing self-reported severity of symptoms in carpal tunnel syndrome patients, showing estimated effect sizes and additional explained variance per step.

Predictors	Symptom severity scale (range 1-5)					
	Model 1		Model 2		Model 3	
	B (SE)	β	B (SE)	β	B (SE)	β
Step 1: Patient characteristics and comorbidities						
Age	-.003 (.002)	-.076	-.002 (.002)	-.050	-.001 (.002)	-.020
Male (reference female)	-.091 (.057)	-.145	-.068 (.053)	-.109	-.059 (.050)	-.094
BMI	.002 (.005)	.015	.004 (.005)	.035	.002 (.004)	.017
Smoking	**.209 (.064)**	**.331****	**.136 (.060)**	**.216***	.109 (.056)	.172
Alcohol usage	-.037 (.050)	-.058	-.007 (.047)	-.010	-.003 (.043)	-.006
Workload (reference: not working)	/	/	/	/	/	/
Light physical work	-.091 (.072)	-.145	-.015 (.068)	-.023	-.052 (.064)	-.083
Moderate physical work	.030 (.067)	.047	.053 (.063)	.084	-.005 (.059)	-.009
Heavy physical work	.070 (.087)	.111	.080 (.081)	.127	.017 (.076)	.027
Duration of symptoms	.001 (.001)	.065	**.001 (.001)**	**.080***	**.001 (.000)**	**.089****
Diabetes Mellitus	.097 (.098)	.155	.044 (.091)	.070	-.006 (.085)	-.009
Rheumatic diseases	**.409 (.117)**	**.649*****	**.405 (.109)**	**.644*****	**.303 (.103)**	**.480****
Trigger finger	.014 (.070)	.023	.005 (.065)	.008	-.018 (.061)	-.029
CMC1 osteoarthritis	.048 (.096)	.077	.046 (.089)	.074	.032 (.083)	.050
Dupuytren's disease	.131 (.144)	.208	-.005 (.136)	-.007	.062 (.126)	.098
De Quervain tenosynovitis	.054 (.191)	.085	.109 (.179)	.174	.054 (.166)	.086
Trauma of the hand/wrist	.193 (.120)	.306	.142 (.112)	.225	.192 (.105)	.304
Instability and/or osteoarthritis of the wrist	-.231 (.138)	-.367	-.229 (.129)	-.364	**-.271 (.120)**	**-.429***
Hypothyroidism	-.021 (.115)	-.034	-.097 (.107)	-.153	-.045 (.101)	-.071
Other nerve compressions	.153 (.132)	.242	.031 (.124)	.049	.080 (.115)	.127
Step 2: Psychological distress and pain catastrophizing						
Psychological distress			.013 (.011)	.048	.002 (.010)	.009
Pain catastrophizing			**.019 (.002)**	**.334*****	**.010 (.003)**	**.180*****
Step 3: Illness perceptions						
Consequences					**.032 (.012)**	**.117****
Timeline					-.014 (.009)	-.059
Control (personal)					-.015 (.008)	-.061
Control (treatment)					.019 (.016)	.043
Identity					**.065 (.011)**	**.248*****
Concern					.003 (.010)	.014
Illness comprehensibility					-.002 (.010	-.008
Emotional representation					**.022 (.009)**	**.109***
R^2	.083		.203		.329	
Adjusted R^2	.055		.177		.299	

Bold indicates a significant association. * P < .05, ** P < .01,*** P < .001, B = unstandardized beta coefficient, β = standardized beta coefficient (for categorical predictors only the outcome was standardized), SE = standard error

Total added variance by psychological distress, pain catastrophizing and illness perceptions was 20% and 25% for the FSS and SSS score, respectively.

Multivariable associations between self-reported severity and psychological factors

In the first model that included patient characteristics and comorbidities, smoking and rheumatic diseases were associated with a higher FSS score. BMI, smoking, duration of symptoms, diabetes mellitus, rheumatic diseases, trigger finger and trauma of the hand/wrist were associated with a higher SSS score, while male sex was associated with a lower SSS score.

Addition of psychological distress and pain catastrophizing (model 2) to the analysis mainly reduced the effect of smoking on the SSS and FSS, while the (standardized) beta coefficients of the other associated patient characteristics remained similar. Also, in contrast to the first model, in the second model the duration of symptoms showed a significant association with the SSS. Pain catastrophizing was significantly associated with higher BCTQ scores, whereas psychological distress was only independently associated with a higher FSS score.

In the final multivariable model (model 3), more negative illness perceptions for consequences and identity were significantly associated with higher FSS and SSS scores. In addition, emotional representations were also associated with a higher SSS score. The addition of illness perception reduced the effect of pain catastrophizing on the FSS and SSS by almost half (from .247/.334 to .115/.180, respectively). It also reduced the effect of psychological distress and rheumatic diseases on the FSS and SSS, but to a lesser extent. In the final model, standardized beta coefficients of consequences (.165), identity (.173), psychological distress (.119) and pain catastrophizing (.115) were similar for the FSS score. For the SSS score, identity had the largest standardized beta coefficient (.248) as compared to the other continuous variables. Of the categorical variables, the presence of rheumatic diseases was associated with the largest effect on self-reported severity, i.e. an increase of .379 and .480 SD for the FSS and SSS score, respectively.

All variance inflation factors were lower than 2, suggesting that our models were not influenced by multicollinearity [38].

DISCUSSION

This study shows that patients with CTS scheduled for surgery who are in more psychological distress, who have more catastrophic thoughts about pain, who interpret their illness as having more impact on their life, and attributing more symptoms to the illness, experience their symptoms and hand function to be worse, as compared with patients

who do not. In addition, patients with worse emotional representations of their illness experience their symptoms to be worse. These psychosocial factors explained an additional 20-25% of the variance in the effect of daily functioning and severity of the symptoms of CTS, which demonstrates that differences in self-reported severity in patients with CTS are associated with these factors.

Our findings on the relation between psychological distress and pain catastrophizing on the one hand and daily functioning and severity of the symptoms on the other, are in line with previous studies. Specifically, studies which analyzed pain catastrophizing and self-reported severity of CTS also found an association between these factors [6, 11, 16, 19]. Also, most studies found that depression and anxiety were associated with self-reported severity [7, 11, 14-17], whereas others found no such relationship [6, 19]. The association we found between psychological distress and functional status, but not with symptom severity, might be explained by the fact that patients with more psychological distress may be more anxious to use the affected hand. This may result in worse self-reported function but may have less impact on self-reported symptoms. However, Shin et al. found a relation between depression (as measured with the Center for Epidemiologic Studies Depression Scale) and the SSS, but not with the FSS. A possible reason for this is that we used the Patient Health Questionnaire-4, which is a screening tool for psychological distress (which includes anxiety) rather than an instrument for detecting depression, such as the Center for Epidemiologic Studies Depression Scale [39] and the Patient Health Questionnaire-9 [40].

Previous studies have shown an association between illness perceptions and health outcomes for various diseases [22, 24, 41-45]; however, to our knowledge, the relationship between illness perceptions and daily functioning and severity of the symptoms has not yet been investigated. We found that perceived consequences of the disease and illness identity were significantly associated with worse self-reported symptom severity and function, even after adjusting for demographic characteristics, comorbidities and known psychological factors (e.g. psychological distress and pain catastrophizing). In addition, the emotional representation of illness also showed a significant association, but only with self-reported symptom severity. Patients with hand osteoarthritis [22] showed associations with the same illness perceptions when adjusted for age and osteoarthritis pain. Furthermore, similar relations were seen between illness perceptions and rheumatoid arthritis, COPD, psoriasis [24] and patients with knee osteoarthritis who were scheduled for total knee replacement, when adjusted for coping and severity and duration of symptoms [44]. However, Chan et al. [46] studied the relation between illness perceptions and self-reported severity in patients with acute hand injury but found no such relationship. The difference with our findings might be explained by the fact that illnesses which are non-acute/chronic offer patients more time to form illness representations with a subsequent effect on symptom experiences.

The addition of illness perceptions to our hierarchical regression analysis reduced the effect of psychological distress and, especially, pain catastrophizing on both BCTQ scores. This suggests either confounding, or a potential, partial mediational role of illness perceptions or psychological factors on daily functioning and severity of the symptoms. This is in line with studies showing that different coping strategies may partially explain the effects of illness perceptions on disease states [47-49]. Pain catastrophizing behavior can be seen as a maladaptive coping strategy and our data suggest an indirect relationship through negative illness perceptions. Future experimental and longitudinal research is necessary to elucidate this relationship in CTS.

Our findings have important implications for clinical practice and the development of psychosocial interventions for CTS. Physicians should take into account that how patients report their symptoms and function depends (to some extent) on how they perceive their illness and pain catastrophizing. Therefore, counseling by the physician on these psychosocial aspects seems warranted in CTS. This is in line with a recent call to promote psychosocial resilience in orthopedic surgical practices [50]. Since psychosocial interventions can change illness perceptions, leading to better outcomes in several illnesses [25, 26], such interventions may also prove useful in CTS. Our findings stress the need for such interventions to address both negative illness perceptions signaling threat like identity and consequences or emotional representations, as well as pain catastrophizing behavior and psychological distress.

The strengths of this study include its large sample size and the use of a comprehensive set of validated questionnaires for clinical severity and psychological factors. However, although the Patient Health Questionnaire-4 is a valid screening tool for psychological distress [31], it lacks the conceptual depth of more extensive questionnaires to assess anxious and depressive states (e.g. Hospital Anxiety and Depression Scale, Center for Epidemiologic Studies Depression Scale). This might have caused the weaker relationship we found between Patient Health Questionnaire-4 score and BCTQ scores as compared to others [7, 14]. Second, we could not analyze the relation between self-reported severity and an objective measure of CTS (e.g. electrodiagnostic testing) because electrodiagnostic testing was not performed in all patients. Furthermore, in patients in whom it was performed, findings were not reported in a consistent and standardized format and the quality was not sufficient for analysis as it was not performed by neurophysiologists. Current literature [6-10] is inconclusive as to whether electrodiagnostic test findings are associated with patient-reported outcome measures, therefore future studies may shed more light on its relationship when controlling for illness perceptions and other psychological factors. Third, this study sample consisted of patients scheduled for a carpal tunnel release, because carpal tunnel release is a primary treatment option. However, patients electing for surgery usually have more severe symptoms than patients who start with a nonoperative treatment. Also, due to the need for surgery, the illness may seem more or

less threatening. Since both these aspects may have influenced how patients perceive their illness, our results may not be generalizable to patients at a different stage of their disease. Although we did not find significant differences in baseline patient characteristics in our non-responder analysis, we also cannot rule out any form of selection bias introduced by patients who did not fill out all psychological questionnaires.

Furthermore, 20-25% of the variance in BCTQ scores could be explained by illness perceptions, psychological distress and pain catastrophizing; this is similar to other studies that analyzed the relative contribution of illness perceptions to health outcomes [23, 41]. However, since a large part of how CTS patients report their symptoms and function remains unexplained, future research needs to identify other factors that might influence how patients report their symptoms. Lastly, because of the cross-sectional study design, it is impossible to determine the direction of the relationship between self-reported severity of CTS and psychosocial factors. As the direction may be bidirectional, future studies should further examine this.

In conclusion, this study shows that psychological distress, pain catastrophizing and the illness perceptions consequence, identity and emotional representation, all play an independent role in self-reported severity of CTS. These psychological factors explained 20% and 25% of variance in the effect on daily functioning and severity of the symptoms of CTS, respectively, indicating their importance in self-reported severity. Clinicians should take this into account when they are consulted by patients with CTS. Future studies should examine whether interventions for illness perceptions may positively influence how patients experience their symptoms. In addition, the relation between illness perceptions and the outcome of carpal tunnel release should be examined.

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Supplementary Table 1. Non-responder analysis between patients who completed all questionnaires and patients who did not respond to (at least) one of the psychosocial questionnaires. At intake, patient characteristics and the FSS/SSS were compared.

Patient Characteristics		Non-responder analysis (N=859)		
		Responders (n=674)	Non-responders (n=185)	
Categorical Variables		%	%	**P-value**
Sex	**Female**	70	78	*.06*
Operated hand	**Right**	57	62	*.30*
Smoking		18	13	*.33*
Alcohol usage		53	61	*.25*
Workload	**No work**	32	36	*.66*
	Light physical work	21	21	
	Moderate physical work	32	32	
	Heavy physical work	15	11	
Dominance	**Left**	6	8	*.42*
	Right	91	90	
	Co-dominant	3	2	
Continuous Variables		**Responders (n=674)**	**Non-responders (n=185)**	
		Mean ± SD	*Mean ± SD*	**P-value**
Age (years)		54.5 ± 13.9	54.2 ± 13.8	*.83*
BMI (kg/m^2)		27.6 ± 4.9	28.4 ± 6.4	*.34*
BCTQ (1-5)	**Functional severity scale**	2.35 ± 0.8	2.45 ± 0.9	*.18*
	Symptom severity scale	2.87 ± 0.6	2.89 ± 0.7	*.79*
Duration of complaints in months		22.6 ± 41.5	22.6 ± 58.8	*.53*

BCTQ = Boston Carpal Tunnel Questionnaire

6 | The influence of illness perception and mental health on return to work after carpal tunnel release

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ABSTRACT

Purpose

Although multiple factors influencing return to work after a carpal tunnel release (CTR) have been identified, little is known about the influence of psychological patient factors on return to work. Therefore, this study aims to identify which psychological factors play a role in the return to work after a CTR.

Methods

Patients planned for a CTR were asked to fill out the Brief Illness Perception Questionnaire (Brief IPQ) and the Patient Health Questionnaire (PHQ-4) preoperatively to measure illness perception and mental health status respectively. Return to work was defined as the time until returning to work for 50% of normal hours and was measured using a questionnaire at six weeks, three months, and six months. To identify associations between non-psychological and psychological patient factors and the return to work after a CTR, a Cox proportional hazards model was constructed.

Results

In total, 615 patients were included in our study. Six months postoperatively, 91% of the patients returned to work. For the psychological patient factors, we found that an increase of one point on the item worrying about CTS and on the item having faith preoperatively in a beneficial effect of the CTR was associated with a hazard ratio (HR) of 0.92 95%CI[0.88 – 0.96] and 1.10 95%CI[1.02 – 1.19] for returning to work in the first six months postoperatively respectively. An increase of one point on the depression subscale of the PHQ-4 was associated with an HR of 0.88 95%CI[0.78 – 0.99] for returning to work in the first six months postoperatively.

Conclusions

Our study showed that multiple psychological patient factors are associated with return to work after a CTR. Addressing these psychological factors preoperatively might be low-cost interventions to improve return to work after carpal tunnel release.

Level of evidence: II

INTRODUCTION

Because of the high prevalence of carpal tunnel syndrome (CTS) in the population[1,2], there are high costs worldwide due to both treatment costs and work disability[3,4]. Furthermore,

to resolve symptoms and prevent further progression of CTS, some patients require a carpal tunnel release (CTR). It has been estimated that around 1.9% of men and 4.1% of women undergo a CTR during their lifetime[5]. Furthermore, in the United States alone, this procedure is performed around 580.000 times annually[6] and costs over 2 billion dollars each year[7]. However, indirect costs due to the absence from work are even higher, as stated by Foley et al.[3], who estimated a loss of earnings of $7500-$14833 per year per CTS patient in the United States.

Multiple factors influencing the return to work after a CTR have been identified, including surgery-related factors, comorbidities, preoperative symptom severity, and work-related factors[8-10]. For example, the average return to work for patients with an occupation demanding heavy physical labor is 14 days longer compared to patients whose occupation does not demand heavy physical labor[9]. Considering comorbidities and surgery-related factors, undergoing a CTR without associated surgery (other procedures performed on the hand at the same time as the CTR) compared to undergoing a CTR with associated surgery, and undergoing a unilateral release compared to a bilateral release, is associated with a hazard ratio (HR) of 1.37 and 1.41 respectively for returning to work in the first 24 months after CTR[11]. This means that the probability of returning to work in the first 24 months after CTR is 1.37 and 1.41 times higher for these patient groups. The hazard ratio is the ratio between the probability of an event occurring (returning to work) in a specific group compared to the probability of an event occurring in another group and can be used to see if patients in a specific group progress faster or slower compared to other groups of patient. Although it has been shown that psychological factors such as illness perception, psychological distress and symptom catastrophizing are associated with treatment outcome[12,13], little is known about the influence of psychological factors on return to work after a CTR.

Therefore, this study aimed to identify which psychological factors play a role in the return to work after a CTR. More insight into these factors might allow for better counselling or enable specific postoperative guidance.

METHOD

Study sample

All patients that underwent a primary CTR between September 2017 and November 2019 in a specialized hand clinic (Xpert Clinic, the Netherlands) were asked to complete online questionnaires at intake, six weeks, three months and six months after surgery. Patients were diagnosed with CTS by a physician based on symptoms and physical examination. When needed, electrodiagnostic testing was performed to reinforce the diagnosis. Patients were planned for surgery after non-surgicalmeasures failed. Patients were included

when they underwent a unilateral primary CTR, did not receive any other CTR in the first six months postoperatively, had paid employment at the time of intake and six months postoperatively, and provided information about return to work at least once at six weeks, three months, or six months following CTR. Furthermore, we selected patients who maintained their original working duties postoperatively and did not adjust to lighter working duties.

If a patient had returned to work, the patient was considered to have reached an endpoint in our analyses. At every next time point (six weeks, three months, six months), we therefore only further analyzed data from patients who had not returned to work at an earlier timepoint or were non-responders at earlier timepoints. This study was approved by the local institutional review board and written informed consent was obtained from all patients. We adhered to the STROBE-guidelines[14].

Treatment

All patients received an open CTR and standard postoperative care, which consisted of bandages and a sling around the operated hand for three to five days. Furthermore, standardized hand therapy was started by a hand therapist postoperatively, consisting of nerve and tendon gliding exercises. Next, patients were seen at our outpatient to monitor progress and to remove sutures within fourteen days postoperatively. Hand therapists at Xpert clinic are instructed to provide similar advice to all patients. Specific actions such as pulling, pushing and loading weight on the operated hand are discouraged for ten to fourteen days. Patients were able to decide when return to work was possible for their occupation based on their postoperative complaints and in consultation with the occupational therapist when necessary.

Measurements

Baseline demographic information was collected from all patients, including sex age, and the dominance of the operated hand. Furthermore, patient-reported outcome measures were collected, including the duration of symptoms, occupation type, EQ5D-index score[15], and Boston Carpal Tunnel Questionnaire(BCTQ)[16] scores. The EQ5D is a measure of general health reflected in a score between zero and one in which a higher score indicates better general health. Patients classified their occupation type based on the physical intensity of their occupation in three categories; light physical work (i.e. an office job), moderate physical work (i.e. working in a shop), and heavy physical work (i.e. working at a construction site).

In addition, information on preoperative psychological factors was collected by administering the Brief Illness Perception Questionnaire (Brief IPQ)[17] and the shortened Patient Health Questionnaire (PHQ-4)[18] in the Dutch language.

The Brief IPQ is validated questionnaire that[19] consists of eight questions on different aspects of the illness perception of the patient. Depending on the amount they agree with a specific statement about their illness, patients rate different illness perceptions on a scale from zero (do not agree at all) to ten (fully agree).

The PHQ-4 is a validated questionnaire[20] that consists of four questions and can be used as a screening method for the mental health of patients in terms of anxiety and depression. Patients score how often they have experienced different statements mentioned by the PHQ-4 about anxiety and depression in the past fourteen days. Each statement is scored on a scale from zero to three, depending on if they have experienced the specific statement in the last fourteen days; not at all (0 points), several days (1), the majority of the days (2) or every day (3). A lower score on the PHQ-4 indicates a better mental health status. Furthermore, the PHQ-4 can be divided into subscales for anxiety and depression[18]. The anxiety subscale score is calculated by the sum of the score of the first two questions of the PHQ-4, the depression subscale score as the sum of the score of the third and fourth question.

Return to work

Patients were asked to fill in an online questionnaire on return to work at six weeks, three months, and six months postoperatively. This questionnaire consisted of five questions:

1) whether the patient is able to work and if not, whether this is due to their hand disorder;
2) how many hours a week the patient is normally employed;
3) how many hours the patient is currently working;
4) If the patient performs their normal work activities or whether adjustments in work activities were made;
5) If applicable, how many weeks postoperatively the patient returned to performing their original working activities.

We defined that patients have returned to work if they returned to performing their usual work for at least 50% of the number of hours in their normal work week. We chose this cut-off point of 50% because, according to Dutch labor law, to meet the requirements to receive any form of compensation, patients should be able to perform less than 50% of their usual work activities. Considering sick leave, in the Netherlands, employers are obligated by law to pay a minimum of 70% of the salary to their employee for a maximum of one year. While these laws determine the minimum conditions for sick leave in the Netherlands, better conditions are possible depending on the collective agreement of the workplace.

Statistical analysis

To identify psychological patient factors influencing the return to work, we created a Cox-model with the time to return to work as the dependent variable. By collecting information on the return to work at different time points within the first six months postoperatively, we are able to create a Cox-model and examine which factors are associated with the return to work in the first six months postoperative.

The Cox proportional hazards model is a statistical technique to evaluate the association of specific factors with the occurrence of a specific event at a particular time by calculating hazard ratio's for individual variables. If the criteria for the assumption of proportional hazards for the Cox-model are met, we can assume that the effect of the individual covariates on the occurrence of the event is the same on every time point during the follow-up time. Furthermore, the Cox-model is able to deal with patients lost to follow up and differences in the amount of follow-up between patients by censoring.

For the independent variables, we included the baseline characteristics age, sex, dominance of the operated hand, occupation type, the symptom severity scale score of the BCTQ, the functional status scale score of the BCTQ, the EQ5D-index score, the Brief IPQ-score and the subscores of the PHQ-4. Moreover, because for some items of the brief IPQ, a high score reflects a relatively optimistic illness perception, while for other items a high score reflects a relatively pessimistic illness perception, in our opinion, the summation score might not always be a reliable measurement of illness perception and might be more difficult to interpret. Therefore, we use the separate items of the Brief IPQ in the Cox model. By implementing the separate items in a single model, we could adjust for them when looking at relationships. This way, we could determine if an item is associated with the return to work, independent of the values of the other items.

Patients were censored in our analysis when they reached retirement or did not complete any other additional questionnaires on return to work during follow up. Considering our Cox model, the criteria for the proportional hazards assumption were met. We considered a p-value smaller than 0.05 as statistically significant.

In addition, based on the collected data, Kaplan-Meier plots were created by plotting the fraction of patients that have returned to work for at least 50% of their working hours at all timepoints.

RESULTS

In total, 819 patients provided information at baseline and were eligible for inclusion, of which 204 were non-responders. Therefore, 615 patients were included. Our analysis showed no significant differences in the demographic characteristics of those who did and did not respond (Supplementary Table 1).

Table 1. Baseline characteristics of the study population (n=615).

Baseline Characteristics		Study population (n=615)
Categorical Variables		***(%)***
Gender	Female	74
Operated hand	Dominant hand	61
Occupational Intensity	Light physical work (i.e. an office job)	32
	Moderate physical work (i.e. working in a shop)	47
	Heavy physical work (i.e. working at a construction site).	21
Continuous Variables		***Mean ± SD***
Age in years		50.0 ± 11.2
Duration of complaints in weeks		20.6 ± 29.2
EQ5D-index score		0.71 ± 0.20
Boston Carpal Tunnel Questionnaire (BCTQ)	Symptom severity scale* (score 1-5)	2.9 ± 0.7
	Functional severity scale* (score 1-5)	2.4 ± 0.8
Brief Illness Perception Questionnaire (Brief IPQ)	How much does your illness affect your life? (score 0-10)	7.0± 2.2
	How long do you think your illness will continue? (score 0-10)	4.7 ± 2.4
	How much control do you feel you have over your illness? (score 0-10)	4.0 ± 2.4
	How much do you think your treatment can help your illness? (score 0-10)	8.6 ± 1.3
	How much do you experience symptoms from your illness? (score 0-10)	6.7 ± 2.2
	How concerned are you about your illness? (score 0-10)	5.6 ± 2.7
	How well do you feel you understand your illness? (score 0-10)	8.1 ± 2.1
	How much does your illness affect you emotionally? (score 0-10)	4.5 ± 2.9
Patient Health Questionnaire (PHQ-4)	Feeling nervous, anxious or on edge (score 0-3)	1.4 ± 0.7
	Not being able to stop or control worrying (score 0-3)	1.4 ± 0.7
	Subscale anxiety (score 0-6)	2.8 ± 1.4
	Feeling down, depressed or hopeless (score 0-3)	1.4 ± 0.7
	Little interest or pleasure in doing things (score 0-3)	1.3 ± 0.6
	Subscale depression (score 0-6)	2.6 ± 1.2

At every time point, we only used data from patients who had not returned to work or were non-responders at earlier timepoints. Therefore, 315, 189 and 76 patients were included at the six weeks, three months, and six months time points, respectively. During follow-up, none of these patients retired. Baseline characteristics are shown in Table 1.

Return to work

Six months postoperatively, 91% of patients returned to work. The median time [Q1,Q3] until return to work was 4 weeks [2 weeks,7 weeks]. The Kaplan-Meier curve for the return to work is shown in Figure 1.

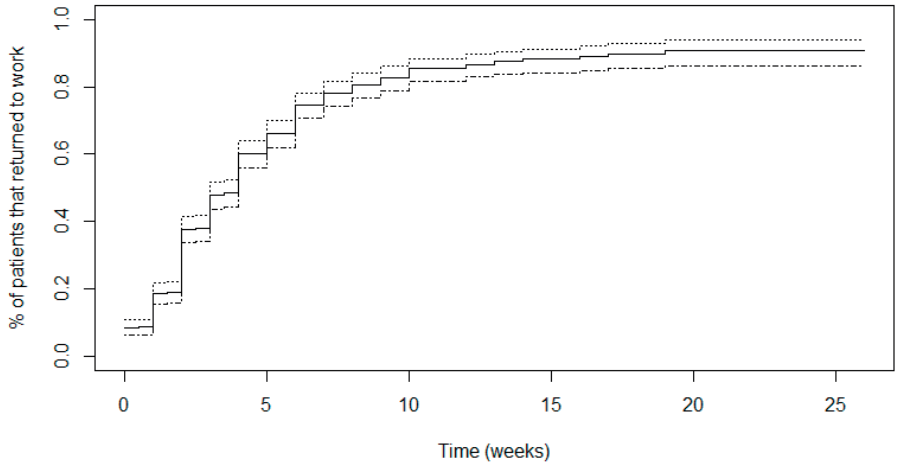


Figure 1. Kaplan-Meier plot for the percentage of patients that have returned to work for 50% of the original contract hours in the first six months after CTR for all included patients with the 95% confidence interval.

Preoperative factors

The Cox model is shown in Table 2. Patients with a higher EQ5D-index score (score 0-1) preoperatively returned to work earlier after a CTR. An increase of 0.1 points of the EQ5D-index score was associated with an HR of 1.16 95%CI[1.09,1.24], meaning the probability of returning to work on any time point in the first six months increased 16%.

Occupations with moderate (HR 0.44, 95%CI[0.36–0.55]) or heavy physical labor (HR 0.30, 95%CI[0.23–0.40]) were associated with a prolonged absence from work after CTR compared to light physical labor. The probability of returning to work on any time point in the first six months postoperatively is 70% lower for heavy physical labor compared to light physical labor.

Receiving a CTR on the dominant hand was associated with a prolonged absence from work (HR 0.73 95%CI[0.61–0.88]); the probability of returning to work on any time point in the first six months postoperative was 27% lower when CTR is performed on the dominant hand compared to the non-dominant hand.

Preoperative Brief-IPQ and PHQ-4

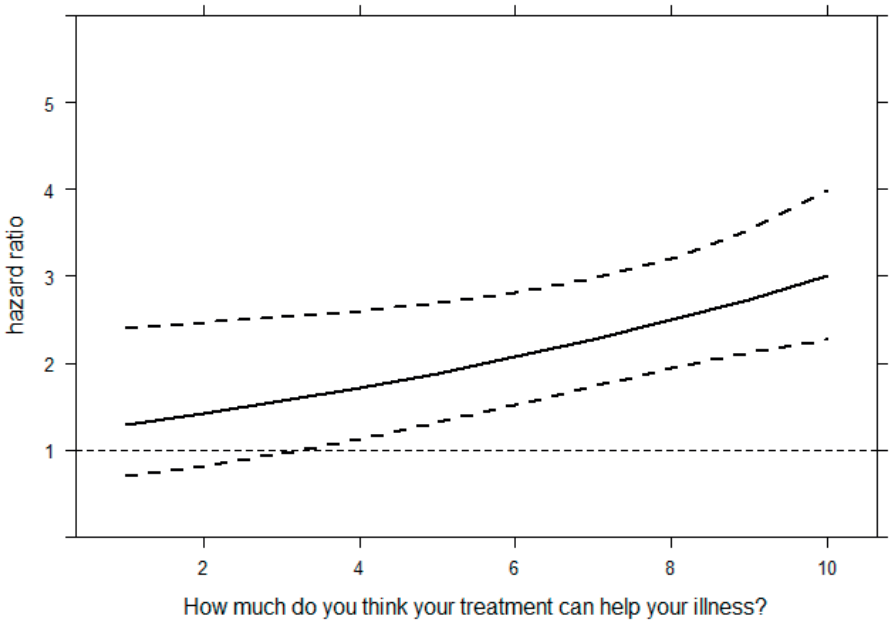
Considering illness perception, patients who believed preoperatively that a CTR will significantly improve CTS complaints tended to return to work earlier (Figure 2A and 3A). An increase of one point on this item (0-10) of the Brief-IPQ is associated with an HR of 1.10 95%CI[1.02–1.19], meaning the probability of returning to work on any time point in the first six months postoperative increased 10%.

Patients who were more concerned with their CTS tended to have a prolonged absence from work after CTR (Figure 2B and 3B). An increase of one point on this item (0-10) of the

Table 2. Cox proportional hazards model with returning to work as the dependent variable and the non-psychological- and psychological patient characteristics preoperative at baseline as independent variables. In this table, the estimate is the natural logarithm of the hazard ratio. For example, a score of eight out of ten points on the item of the brief-IPQ 'How much do you think your treatment can help your illness?' will result in an estimate of 8 * 0.094 = 0.752. To calculate the HR from this estimate, we then calculate HR = $e^{0.752}$ = 2.12. This means that the hazard of returning to work for this patient on a specific moment in time is 112% higher than if this patient would have scored zero points on this item.

	Estimate (Ln(HR))	Hazard Ratio	Confidence Interval	p-value
Non-psychological patient factors				
Age in years	<-0.001	1.000	[0.991 – 1.008]	0.970
Duration of complaints in weeks	0.002	1.002	[0.999 – 1.005]	0.222
Gender				
Male	Reference	Reference	Reference	Reference
Female	-0.204	0.815	[0.655 – 1.015]	0.068
Workload				
Light physical labour	Reference	Reference	Reference	Reference
Medium physical labour	-0.802	0.448	[0.364 – 0.553]	**<0.001**
Heavy physical labour	-1.197	0.302	[0.228 – 0.401]	**<0.001**
Dominant hand treated				
No	Reference	Reference	Reference	Reference
Yes	-0.312	0.732	[0.607 – 0.884]	**0.001**
EQ5D index score (0-1)	1.523	4.585	[2.435 – 8.635]	**<0.001**
BCTQ - SSS (1-5)	0.159	1.172	[0.983 – 1.398]	0.076
BCTQ - FSS (1-5)	-0.061	0.940	[0.809 – 1.094]	0.425
Psychological patient factors				
Brief Illness Perception Questionnaire (0-10)				
How much does your illness affect your life?	0.017	1.017	[0.968 – 1.069]	0.505
How long do you think your illness will continue?	0.005	1.005	[0.962 – 1.049]	0.838
How much control do you feel you have over your illness?	-0.021	0.980	[0.944 – 1.017]	0.277
How much do you think your treatment can help your illness?	0.094	1.098	[1.016 – 1.186]	**0.018**
How much do you experience symptoms from your illness?	-0.017	0.982	[0.933 – 1.035]	0.514
How concerned are you about your illness?	-0.081	0.923	[0.882 – 0.965]	**<0.001**
How well do you feel you understand your illness?	0.007	1.007	[0.959 – 1.058]	0.786
How much does your illness affect you emotionally?	0.016	1.016	[0.974 – 1.061]	0.465
Patient Health Questionnaire (0-6)				
Subscale anxiety	0.084	1.087	[0.986 – 1.199]	0.093
Subscale depression	-0.129	0.879	[0.777 – 0.994]	**0.039**

A


hazard ratio
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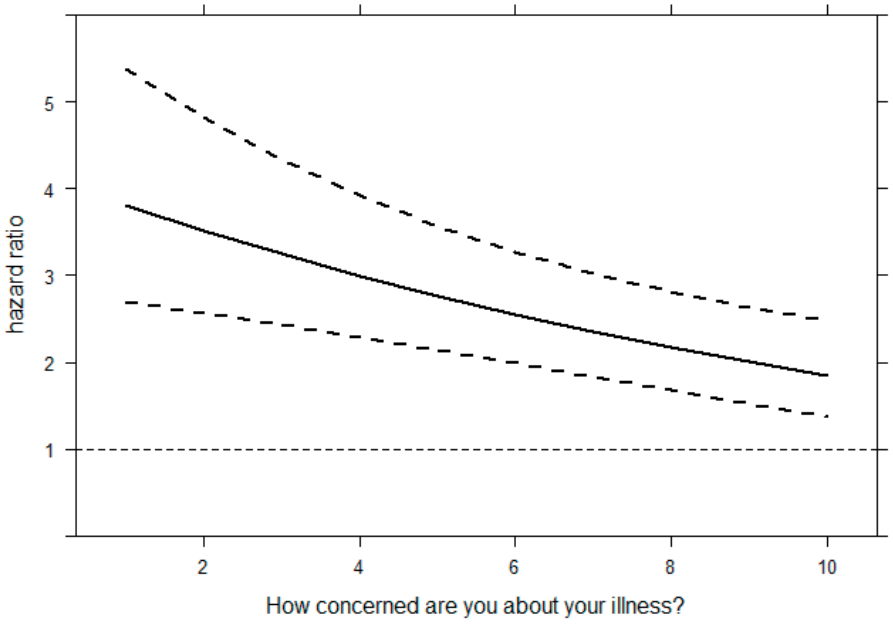
6
8
10
How much do you think your treatment can help your illness?

B


hazard ratio
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10
How concerned are you about your illness?

C

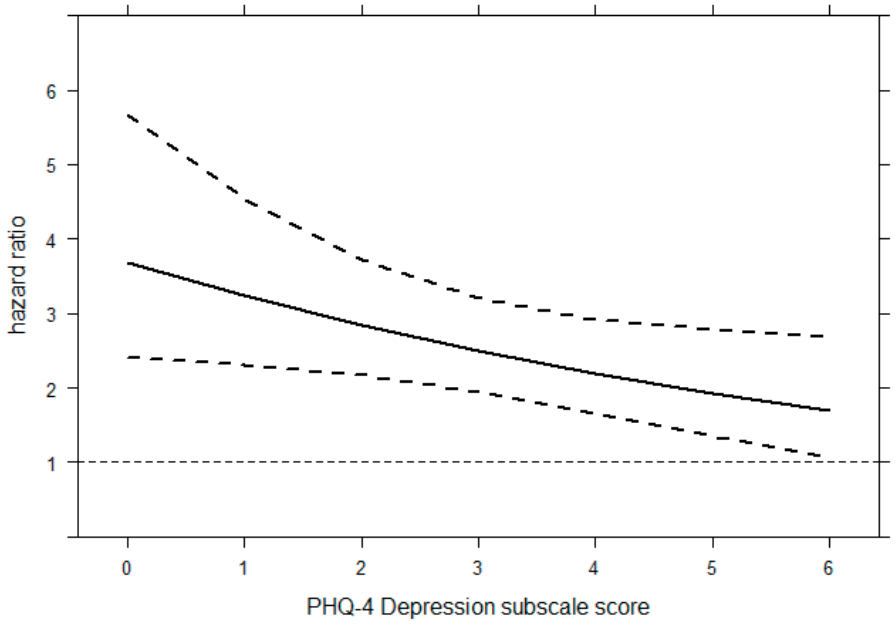
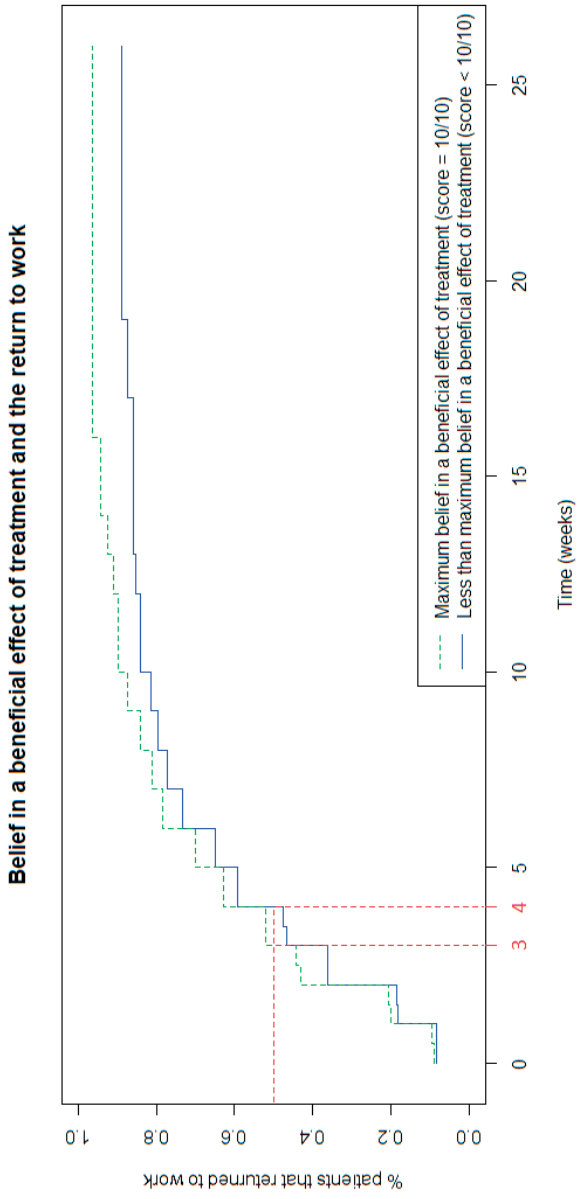
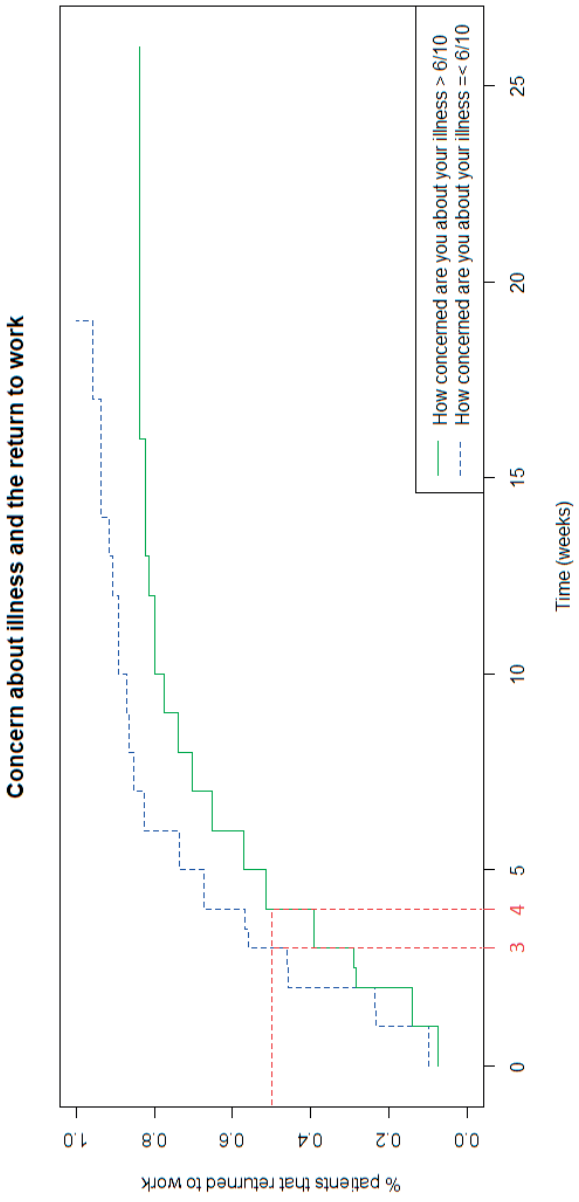


Figure 2A-C. Effect-plots for the different psychological patient factors from the Cox proportional hazards model that are associated with the return to work. The graphs show the hazard ratio for a simulated patient in which the baseline characteristics fixed (in this case, a male with a light physical occupation operated on his dominant hand and with average values of our cohort for all the other baseline characteristics reported in Table 1). The hazard ratio is then shown for the different scores for the factors 'How much do you think your treatment can help your illness' (Figure 2A), 'How concerned are you about your illness' (Figure 2B), and the depression subscale of the PHQ-4 (Figure 2C). The total HR for this patient can be calculated by using Table 2 and can be read as the increase or decrease of the hazard of returning to work on a specific moment in time.

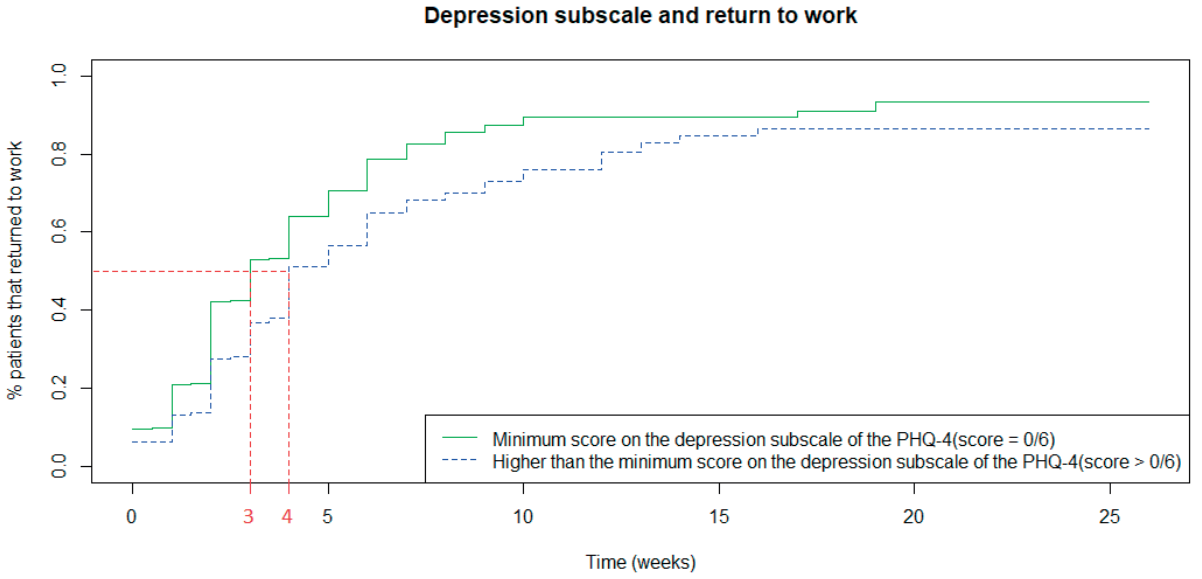
A


Belief in a beneficial effect of treatment and the return to work
% patients that returned to work
0.0
0.2
0.4
0.6
0.8
1.0
0
3
4
5
10
15
20
25
Time (weeks)
Maximum belief in a beneficial effect of treatment (score = 10/10)
Less than maximum belief in a beneficial effect of treatment (score < 10/10)

B


Concern about illness and the return to work
% patients that returned to work
0.0
0.2
0.4
0.6
0.8
1.0
0
3
4
5
10
15
20
25
Time (weeks)
How concerned are you about your illness > 6/10
How concerned are you about your illness =< 6/10

C



Figures 3A-C. Survival analyses comparing subgroups of patients where the total study population is split up based on the median score of the different psychological patient factors from the Cox proportional hazards model that are associated with the return to work. The graphs show for each factor a difference of one week between the split up subgroups for the time that 50% of patients have returned to work. However, the effect of these factors is unadjusted for other factors in these figures.

Brief IPQ was associated with an HR of 0.92 95%CI[0.88–0.96], meaning the probability of returning to work at any time point in the first six months postoperative was decreased by 8%.

Regarding the PHQ-4, a higher score on the depression-subscale was associated with a prolonged absence from work after CTR (Figure 2C and 3C). An increase of one point on this subscale (0-6) was associated with an HR of 0.88 95%CI[0.78–0.99], meaning the probability of returning to work at any time point in the first six months postoperative was decreased 12%.

DISCUSSION

In this study, we showed that the psychological factors of worrying about CTS, believing preoperatively in a beneficial effect of the CTR, and having symptoms of depression are associated with return to work after a CTR during the first six months postoperatively. In addition, we found that other factors such as the preoperative EQ-5D-index score, occupation type, and dominance of the operated hand are also associated with when a patient returns to work.

Considering psychological factors, while Butterfield et al.[21] and Katz et al.[22] did not find an association between depressive symptoms as measured by the Health Status Questionnaire and the 5-item mental health index included in the SF-36 respectively, our study did find an association with depressive symptoms as measured by the PHQ-4. Kho et al.[23] reported an association, in line with our results, between the presence of depression and prolonged absence from work after CTR. Unfortunately, Kho et al.[23] did not report an effect size for the presence of depression and the association with return to work in their model.

While we found an association between depressive symptoms and return to work after a CTR, we did not find a significant association between anxiety, as measured by the PHQ-4, and return to work. This is in contrast with Kho et al.,[23] who did find an association between the presence of anxiety and return to work after a CTR. However, Kho et al.[23] did not quantify anxiety with a validated questionnaire and looked at anxiety only in combination with depression.

Concerning the illness perception and the return to work after CTR, little research has been conducted. Similar to this study, Hansen et al.[24] studied the association between the preoperative belief that the CTR would relieve complaints at 3 months postoperatively and return to work. In contrast to our study, they did not find a significant association.

The results of our study are in line with previous studies that occupation type is an important factor for return to work after a CTR[8,11,25,26]. Moreover, our study is in line with the Cox model by Parot-Schenkel et al.[11] that indicated that gender is not associated with return to work, although this association was reported in other studies[8,25]. Furthermore,

we found an association between surgery in the dominant hand and return to work after a CTR. This is in contrast with the findings of Carmona et al.[25], Atroshi et al.[27] and Acharya et al.[28] who did not find this association. This different results might be explained by differences in sample characteristics, statistical techniques, or the return to work definition.

In this study, the median time until return to work was 4 weeks. However, the average return to work ranges from 4 days to 168 days in studies reporting the return to work after a CTR[29]. An explanation for this broad range might be the distribution of occupation types within the different cohorts or the availability of paid sick leave. Moreover, Parot-Schenkel et al.[11] analyzed factors influencing the return to work after a CTR in a relatively large cohort by constructing a Cox model as well. They found that having a bilateral release, having a subjective presumption of work as the cause of CTS, occupational factors, and dissatisfaction with surgery was associated with the return to work. However, this model did not look in depth at illness perception and mental health status of the patients.

Several limitations of our study should be considered. First, our model did not include information on comorbidities, which might have influenced return to work. However, to adjust for this, we asked patients to complete the EQ-5D questionnaire, a measure of general health, preoperatively and added this score in our model. Second, differences in return to work between different occupational groups might be influenced by the recommendation of the surgeon or hand therapist[30]. At Xpert Clinic, recommendation on the return to work is mainly provided by the hand therapist. Hand therapists at Xpert clinic provide similar advice to all patients. Because all patients had a similar postoperative treatment, this would not likely have influenced the hazard ratio's provided by the Cox-models. While this might have influenced the absolute rate of return to work of patients, the ratio between different patients groups will likely be similar when patients receive similar postoperative treament.

Patients were able to decide when return to work was possible for their occupation based on their postoperative complaints and in consultation with an occupational physician when necessary. Although consultation with an occupational physician is rarely the case after CTR and also rare in our study cohort , these occupational physicians can be consulted by employers if there was a prolonged absence of work. Third, we did not take the presence of complications into account for return to work and, fourth, we did not have information on pre-surgical sick leave and this might have influenced the return to work. Fifth, we did not conduct a sample size calculation since sample size calculations for Cox models are largely dependent on simulation studies. These are often not very precise and hard to interpret for other study designs[31].However, based on the narrow confidence intervals for most of the estimates in our models, we can conclude that the models in our study were stable. . Sixth, at Xpert Clinic, standardized hand therapy is started by a hand therapist postoperatively after a CTR. These postoperative treatment guidelines after a CTR might differ with the guidelines of other medical facilities and could, therefore, influ-

ence the generalizability of our results. However, because all our CTR patients underwent the same postoperative hand therapy, this will not likely influence the hazard ratio's that we found in this study because these are ratio's between different groups of patients and all patients have benefitted equally from this postoperative treatment.

In conclusion, this study showed an association between multiple psychological factors and the return to work in the first six months after a CTR. As shown by Shin et al.[32], intervening on psychological status leads to better reported outcomes for CTS. Therefore, addressing the psychological patient factors found in our study preoperatively might lead to low-cost interventions to improve the return to work after a CTR. For example, physicians might focus more on the illness perceptions and mental health of the patient preoperatively and could try to address these factors before surgery. Moreover, physicians might weigh these factors in their decision for surgery. In addition, the results of our study give more insight into the multidimensional nature of return to work after a CTR.

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Supplementary Table 1. Non-responder analysis for the response on providing information on return to work by eligible patients. Statistical testing to test for differences in baseline characteristics between responders and non-responders was done with T-tests and Chi-square tests for continuous and categorical data, respectively. When taking into account multiple testing, no differences between responders and non-responders were found.

Baseline Characteristics		Non-responder analyses (n=819)		
		Responders (n=615)	Non-responders (n=204)	
Categorical Variables		*(%)*	*(%)*	**P-value**
Gender	Female	74	76	0.48
Operated hand	Dominant hand	61	59	0.74
Occupational Intensity	Light physical work (i.e. an office job)	32	43	0.02
	Moderate physical work (i.e. working in a shop)	47	39	
	Heavy physical work (i.e. working at a construction site).	21	18	
Continuous Variables		***Mean ± SD***	***Mean ± SD***	**P-value**
Age in years		50.0 ± 11.2	50.1 ± 11.8	0.94
Duration of complaints in weeks		20.6 ± 29.2	20.0 ± 35.5	0.83
EQ5D-index score		0.71 ± 0.20	0.68 ± 0.23	0.11
Boston Carpal Tunnel Questionnaire (BCTQ)	Symptom severity scale* (score 1-5)	2.9 ± 0.7	2.9 ± 0.7	0.97
	Functional severity scale* (score 1-5)	2.4 ± 0.8	2.5 ± 0.9	0.14
Brief Illness Perception Questionnaire (Brief IPQ)	How much does your illness affect your life? (score 0-10)	7.0 ± 2.2	7.1 ± 2.1	0.37
	How long do you think your illness will continue? (score 0-10)	4.7 ± 2.4	4.7 ± 2.1	0.56
	How much control do you feel you have over your illness? (score 0-10)	4.0 ± 2.4	4.1 ± 2.6	0.50
	How much do you think your treatment can help your illness? (score 0-10)	8.6 ± 1.3	8.5 ± 1.6	0.66
	How much do you experience symptoms from your illness? (score 0-10)	6.7 ± 2.2	6.6 ± 2.5	0.58
	How concerned are you about your illness? (score 0-10)	5.6 ± 2.7	5.7 ± 2.7	0.61
	How well do you feel you understand your illness? (score 0-10)	8.1 ± 2.1	8.1 ± 1.9	0.88
	How much does your illness affect you emotionally? (score 0-10)	4.5 ± 2.9	4.9 ± 3.1	0.20
Patient Health Questionnaire (PHQ-4)	Subscale anxiety (score 0-6)	2.8 ± 1.4	3.0 ± 1.5	0.07
	Subscale depression (score 0-6)	2.6 ± 1.2	2.9 ± 1.5	0.02

PART 3

FACTORS INFLUENCING TREATMENT OUTCOME AFTER SURGICAL TREATMENT OF SECONDARY CARPAL TUNNEL SYNDROME

7 | Outcome of revision carpal tunnel release in comparison to primary carpal tunnel release

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In submission

ABSTRACT

Background

Although carpal tunnel release (CTR) is often successful, revision surgery seems less effective than primary surgery, but this has never been investigated by comparing these outcomes in otherwise similar cohorts. Therefore, the aim of this study was to compare the outcome of primary CTR and revision CTR in all patients with carpal tunnel syndrome (CTS) and when corrected for baseline severity and demographics.

Methods

A total of 903 hands of primary CTS patients and 132 hands of recalcitrant CTS patients underwent CTR in one of the 18 specialized hand clinics between 2012 and 2019. Patients completed online questionnaires on demographics, clinical severity, and satisfaction as part of usual care. The primary outcome measure was the Boston Carpal Tunnel Questionnaire (BCTQ), which was administered at intake and six months after surgery. Propensity score matching was used to be able to compare outcome of primary and recalcitrant CTS patients with similar baseline severity and demographics.

Results

The average BCTQ total score at six months was better in primary patients (1.55±0.58) than in recalcitrant patients (1.94±0.73, p=<0.001). In primary and recalcitrant patients match on similar baseline characteristics, the BCTQ total score at six months was also better in primary patients (1.65±0.63) than in recalcitrant patients (1.92±0.73, p=0.002).

Conclusion

This study shows that the outcome after revision CTR is worse compared to the outcome after primary CTR, but the differences are relatively small. Preoperative symptom severity, functional status and demographics may play a role, since correcting for this factors reduces the difference in outcomes between primary and revision CTR. These results can be used for counselling of patients prior to surgery.

INTRODUCTION

Carpal tunnel syndrome (CTS) affects up to 7% of the population and is the most common neuropathy of the upper extremity[1-3]. Although carpal tunnel release (CTR) is successful, up to 31% of patients remain symptomatic or have recurring symptoms, of whom revision surgery is needed in up to 12%[4-9].

The persistence or recurrence of symptoms after CTR has been described as recalcitrant CTS, which is considered to be more difficult to treat than primary CTS[9-11]. Previous studies have shown the outcome for both primary and revision CTR, and when comparing mean outcomes, it seems that primary surgery is more successful in reducing symptoms and improving function[12-15]. For example, Kleermaeker et al.[13] found an average postoperative symptom severity score of 1.54 in primary patients (n=179), while Cobb et al.[14] found an average postoperative symptom severity score of 1.92 in recalcitrant patients (n=132). Demographic and clinical factors may influence this difference, as patients with recalcitrant CTS seem to have higher preoperative symptom severity, worse daily hand functioning, and more comorbidities[16-18].

To our knowledge, no previous research has directly compared the outcome of primary and revision CTR in otherwise similar cohorts, nor investigated which factors may explain a possible difference in outcomes. Obtaining this knowledge could improve preoperative counselling of patients with recalcitrant CTS and create realistic expectations. Therefore, the aim of this study was to compare the mean outcome of primary with revision CTR, both uncorrected and corrected for baseline disease severity and demographic factors. Additionally, subgroup analysis for recurrent and persistent CTS separately was performed.

MATERIALS AND METHODS

Participants

Patients that underwent primary or revision CTR for CTS between January 2012 and May 2019 at one of the 18 specialized hand and wrist surgery clinics in the Netherlands (Xpert Clinic) were selected. As part of routine care, patients were asked to fill out online questionnaires in our web-based surgical outcome registration, GemsTracker © (GEneric Medical Survey Tracker), a secure web-based application for distribution of questionnaires and forms during medical research and quality registrations. The cohort and data collection have previously been reported[19].

Adult patients who completed the outcome questionnaires at baseline and at six months follow up were included. If patients were treated bilaterally both hands were included. Patients with concomitant surgeries of the hand that could influence the outcome measures (e.g., cubital tunnel release, Guyon's canal release, and CMC1 arthroplasty surgery)

were excluded. The study was approved by the local Institutional Review Board. Adequate information was provided. All patients gave written informed consent.

Diagnosis and treatment

Diagnosis and decision for surgery were based on history taking and clinical findings by European board-certified hand surgeons, in concordance with the Dutch guidelines regarding CTS diagnosis and treatment[20]. The surgery performed was an open CTR for all included patients, meaning a release of the flexor retinaculum. Neurolysis, synovectomy or a form of flap surgery (e.g. hypothenar fat flap procedure) were performed in a number of recalcitrant patients, where deemed necessary by the surgeon. Exact data on the additional procedures was not available.

Postoperative care consisted of 3 to 5 days of bandages and a sling around the operated hand. Standardized hand therapy started after this, beginning with tendon gliding exercises followed by exercises for range of motion of the wrist and nerve gliding. Progress was monitored and sutures removed at the postoperative check 14 days after surgery. Thereupon, treatment to minimize scar formation was started, consisting of scar massage and silicone scar sheets (if indicated).

Recurrent and persistent symptoms

Recalcitrant CTS can be divided into two subgroups: patients with either persistent or recurrent symptoms. We classified symptoms as either persistent or recurrent based on the medical history recorded in the medical records. We defined persistent symptoms as occurring within three months after primary surgery, and recurrent symptoms as occurring after three months[12, 21, 22].

Baseline Characteristics

Baseline characteristics were collected at intake and included: age, sex, BMI, hand dominance, operated hand, persistent or recurrent symptoms (revision group), duration of symptoms, comorbidities, concomitant procedures, number of previous CTR's (revision group), workload, smoking status, and alcohol usage.

Comorbidities were divided into two categories: "systemic conditions" and "comorbidities of the hand/wrist". The following comorbidities were classified as "systemic conditions": diabetes mellitus, rheumatic arthritis, fibromyalgia, Sjögren's syndrome, polymyalgia rheumatica, gout, and pregnancy. Comorbidities classified as "comorbidities of the hand/wrist" were: carpometacarpal osteoarthrosis (CMC1 arthrosis), trigger fingers, Dupuytren's disease, Quervain's disease, tendinitis, arthrosis or instability of the wrist, trauma of the wrist, ulnar nerve entrapment, Guyon's tunnel disease, cubital tunnel compression, and pronator teres syndrome.

Primary outcome measurement: BCTQ

The primary outcome measure was the BCTQ total score at six months, using the Boston Carpal Tunnel Questionnaire (BCTQ; 1=no complaints, 5=maximum complaints possible, Dutch-language version) measured at baseline and six months after surgery[23]. The BCTQ is a questionnaire to measure self-reported symptom severity and functional status in patients with CTS[24-26].

The BCTQ contains two subscales: the Symptom Severity Scale (SSS) and Functional Status Scale (FSS). The minimally clinical important difference is a 0.92 points change in the BCTQ total score, and 1.14 and 0.74 for SSS and FSS, respectively[27].

Secondary outcomes

Secondary outcomes were complications and patient satisfaction with the outcome of treatment. Complications recorded during the follow-up period were: infection treated with antibiotics, wound dehiscence, postoperative bleeding, and injury of the median nerve and palmar cutaneous branch.

Patient satisfaction was measured using a questionnaire about satisfaction with the treatment effect at six months follow up on a 5-point scale.

Statistical analysis

Descriptive statistics were calculated for all variables in both subgroups, before and after matching. A proportion of the recalcitrant patients (23% of unmatched patients) had missing values for BMI, smoking status, and alcohol usage due to nonresponse. Since previous research showed these variables are not related to the clinical outcome[15, 17, 28], we continued the analysis without including these characteristics. Baseline characteristics before matching were compared using an unpaired t-test for continuous variables and a chi-square test for categorical variables.

Propensity score matching was used to adjust for potential confounding. Propensity score matching is a matching technique for observational data using propensity scores to estimate the effect of a treatment by accounting for the covariates that predict receiving the treatment[29, 30] and was successfully used previously in patients with hand and wrist disorders[31-33].

The following baseline characteristics were included as covariates for the propensity score: age, sex, workload, dominant side treated, comorbidities, presence of CTS on both sides, and BCTQ subscales at baseline. We matched patients on a 1-to-1 ratio using the nearest-neighbour method with a caliper width of 0.2 SD[34]. The standardized mean difference (SMD) was used to examine the balance of the covariates between the two groups. We aimed for a SMD below the 0.1 threshold for all included covariates[35]. To account for the matched nature of the sample, paired t-tests were performed to study differences in primary outcome[36, 37].

Differences in total complication rate between both groups were calculated using chi-square tests. *Ninety-five % confidence intervals* were calculated for all outcomes and p-*values* less than 0.05 were considered statistically significant. The statistical software package R (version 3.5.2) was used for all analyses and processing of the data.

RESULTS

A total of 903 hands of primary CTS and 132 hands of recalcitrant CTS patients were included. Patients, on average, had a relatively high BMI and were predominantly female (Table 1). Recalcitrant patients had more comorbidities, were less likely to drink alcohol, and had more often bilateral CTS than primary patients. The baseline BCTQ total score, FSS, and SSS subscales showed more severe symptoms in recalcitrant patients, compared to primary patients.

After propensity score matching, both groups contained 128 hands. The balance of the included covariates is represented by the SMD in Table 1. Besides sex and systemic comorbidities, all covariates had a SMD below the predefined threshold.

Figure 1 shows the improvement of the BCTQ total score, FSS and SSS subscales over time for both groups, before and after matching. Before matching, the BCTQ total score at six months was better in primary patients (1.55±0.58) than in recalcitrant patients (1.94±0.73, p=<0.001). Both the FSS and SSS subscales at six months were better in primary patients (1.55±0.63 and 1.55±0.58, respectively) compared to recalcitrant patients (1.93±0.76 and 1.95±0.77, respectively, p=<0.001).

Primary patients improved more on the BCTQ total score than recalcitrant patients. (1.10 vs 0.90, respectively, p=0.003). This difference in improvement was mainly due to more improvement in primary patients in the SSS score (1.32 in primary vs. 1.03 in recalcitrant patients, p=<0.001) and to a lesser extent in the FSS score (0.87 in primary vs. 0.77 in recalcitrant patients, p=0.158)

After matching, the difference between the two groups in BCTQ total scores (1.92 vs. 1.65, p=0.002), FSS (1.67 vs. 1.92, p=0.011) and SSS subscales (1.62 vs. 1.94, p=<0.001) at six months was smaller, but symptoms remained higher in the recalcitrant group. In addition, primary patients also still had more improvement in BCTQ total score (1.18 vs. 0.89, p=0.004), FSS (1.02 vs. 0.75, p=0.013) and SSS (1.34 vs. 1.02, p=0.003) subscales after matching.

Overall, 95% of unmatched primary patients reported an improvement on the BCTQ total score compared to 89% of unmatched recalcitrant patients (p=0.04). This was similar for the matched groups: 95% of primary patients and 89% of recalcitrant patients (p=0.17). Taking into account the minimal clinically important difference, 59% of unmatched primary patients and 50% of unmatched recalcitrant patients reported an improvement

(p=0.05), versus 64% and 48% of primary and recalcitrant matched patients respectively (p=0.02).

Before matching, 18% of primary patients achieved a BCTQ total score of 1 (i.e. no complaints) at six months, compared to 10% of recalcitrant patients (p=0.03). After matching, 17% of primary patients achieved this BCTQ total score of 1 at six months, compared to 10% of recalcitrant patients (p=0.15).

Table 1. Baseline characteristics of the study population, before and after propensity score matching

	Unmatched patients			**Matched patients**		
	Primary n = 903	Revision n = 132	*P value*	Primary n = 128	Revision n = 128	*SMD*
Categorical variables	**Percentage %**			**Percentage %**		
Male Sex	30	23	0.173	30	24	0.123
Comorbidities						
Systemic = present (%)	11	23	<0.001	16	20	0.101
Hand / wrist = present	28	45	<0.001	40	44	0.079
Concomitant procedures						
Present	10	18	0.006	20	16	0.081
Workload						
No work	37	39	0.750	38	39	0.032
Light physical work	22	22	1.000	22	23	0.019
Moderate physical work	28	26	0.643	25	24	0.032
Heavy physical work	13	14	0.966	16	14	0.044
Bilateral CTS	34	54	<0.001	55	52	0.047
Dominance			0.588			
Left	7	9		4	9	
Right	90	86		94	87	
Ambidextrous	4	5		2	4	
Dominant side affected	61	61	1.000	65	60	0.097
Smoking = yes*	18	21	0.649	25	20	0.110
Alcohol usage = yes*	57	45	0.025	59	45	0.277
Continuous variables	**Mean ± SD**			**Mean ± SD**		
Age (y)	55 (12.5)	56 (12.4)	0.509	55 (11.8)	56 (12.5)	0.075
BMI (kg/m^2)*	28 (5.1)	28 (4.9)	0.951	28 (4.8)	28 (4.8)	0.008
BCTQ - intake						
SSS score – intake	2.9 (0.6)	3.0 (0.6)	0.046	3.0 (0.6)	3.0 (0.6)	0.004
FSS score – intake	2.4 (0.8)	2.7 (0.7)	<0.001	2.7 (0.8)	2.7 (0.7)	0.040
Total – intake	2.6 (0.6)	2.8 (0.6)	0.001	2.8 (0.6)	2.8 (0.6)	0.022
Duration of complaints (mo)	26 (52.1)	26 (37.0)	0.968	26 (34.6)	26 (37.5)	0.006
Number of previous CTR's (Revision group)		1.1 (0.4)			1.1 (0.4)	

*Revision group: Smoking/Alcohol usage/BMI, before matching n = 101, after matching n = 98

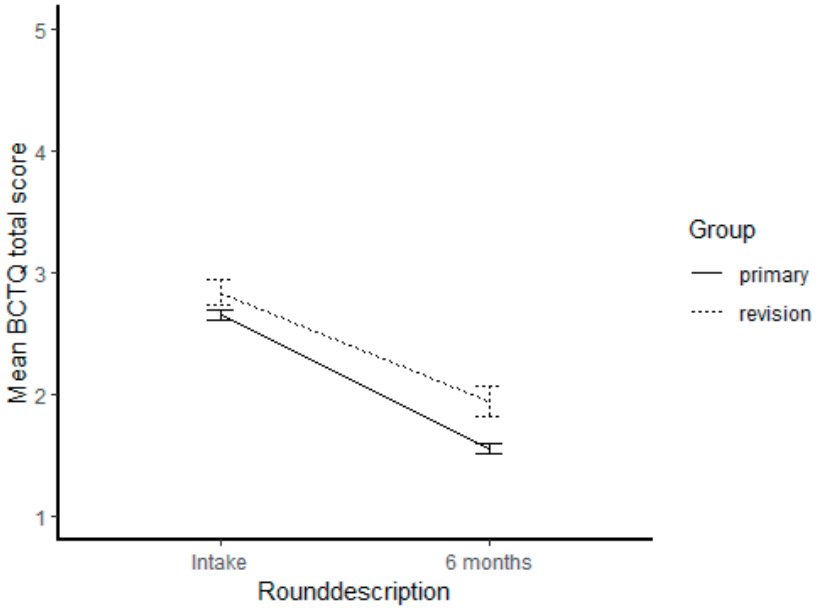

Figure 1A. BCTQ total before matching

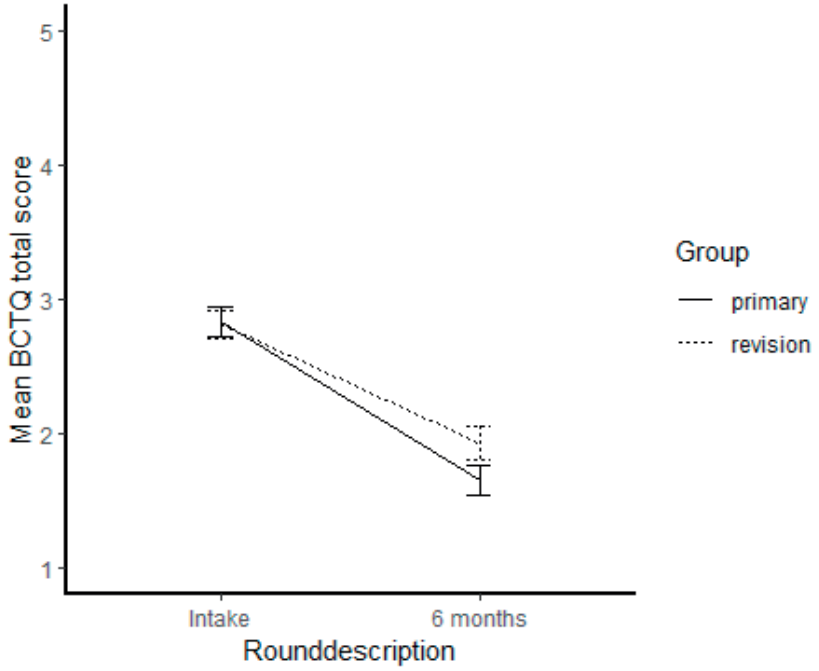

Figure 1B. BCTQ total after matching

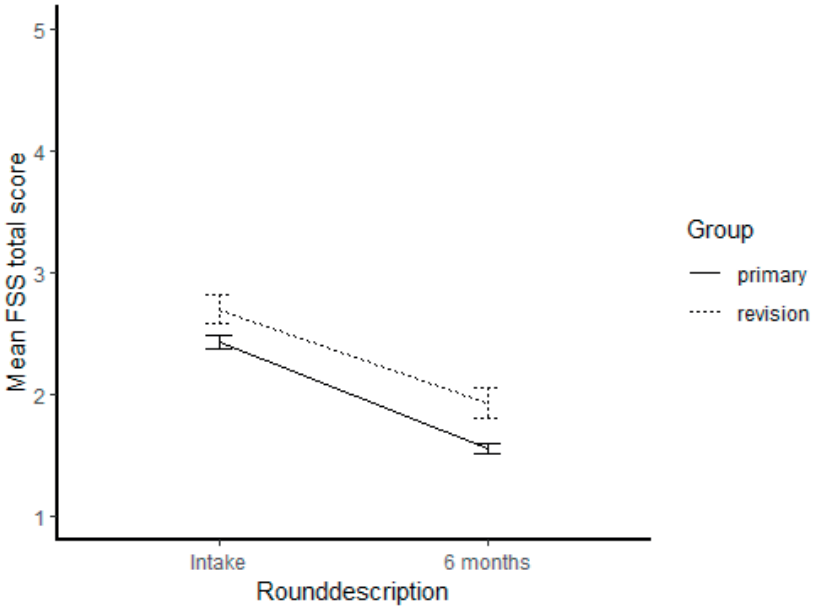

Figure 1C. FSS before matching

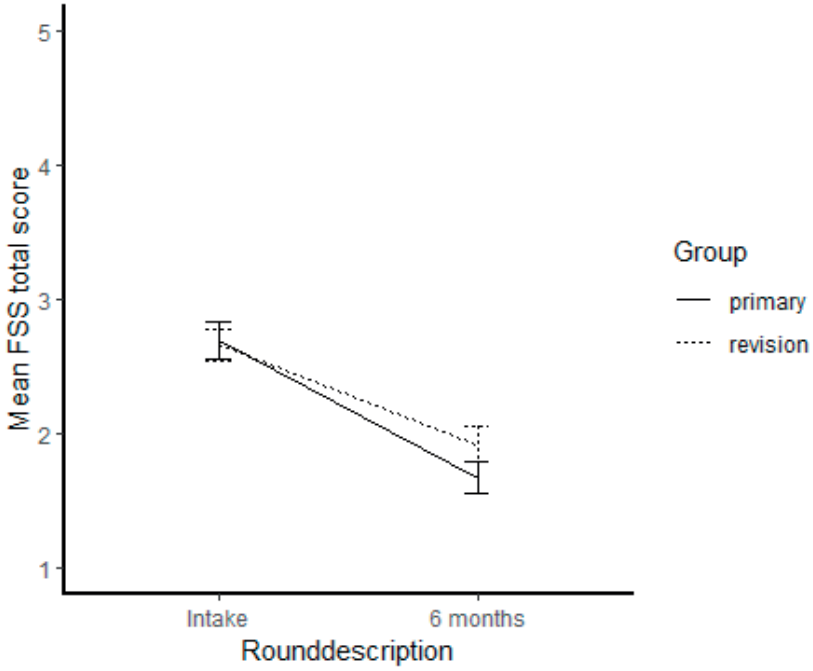

Figure 1D. FSS after matching

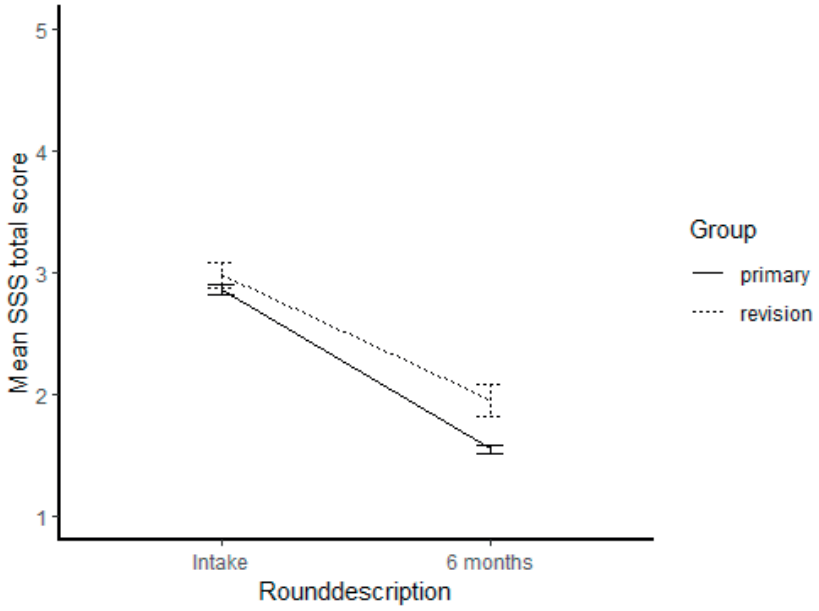

Figure 1E. SSS before matching

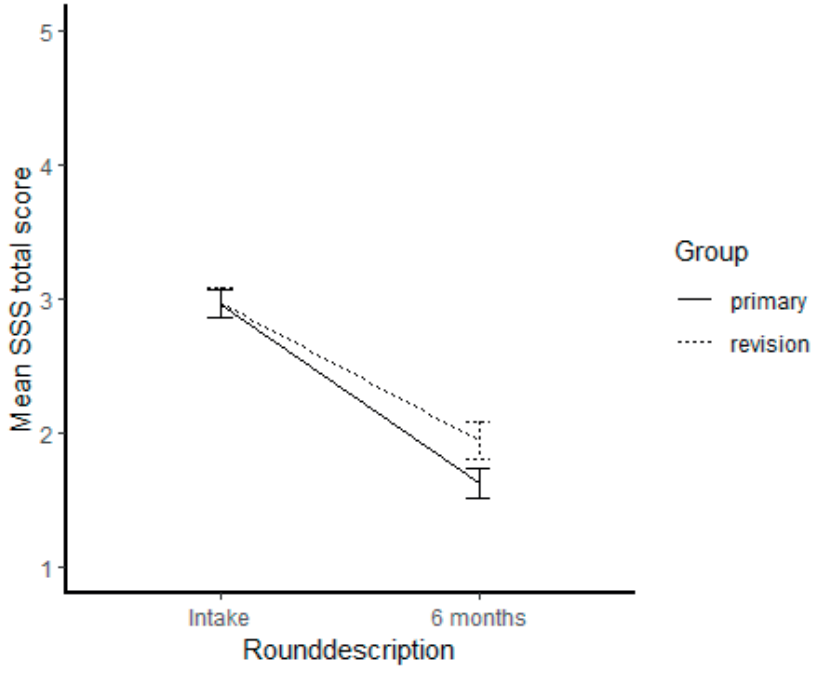

Figure 1F. SSS after matching

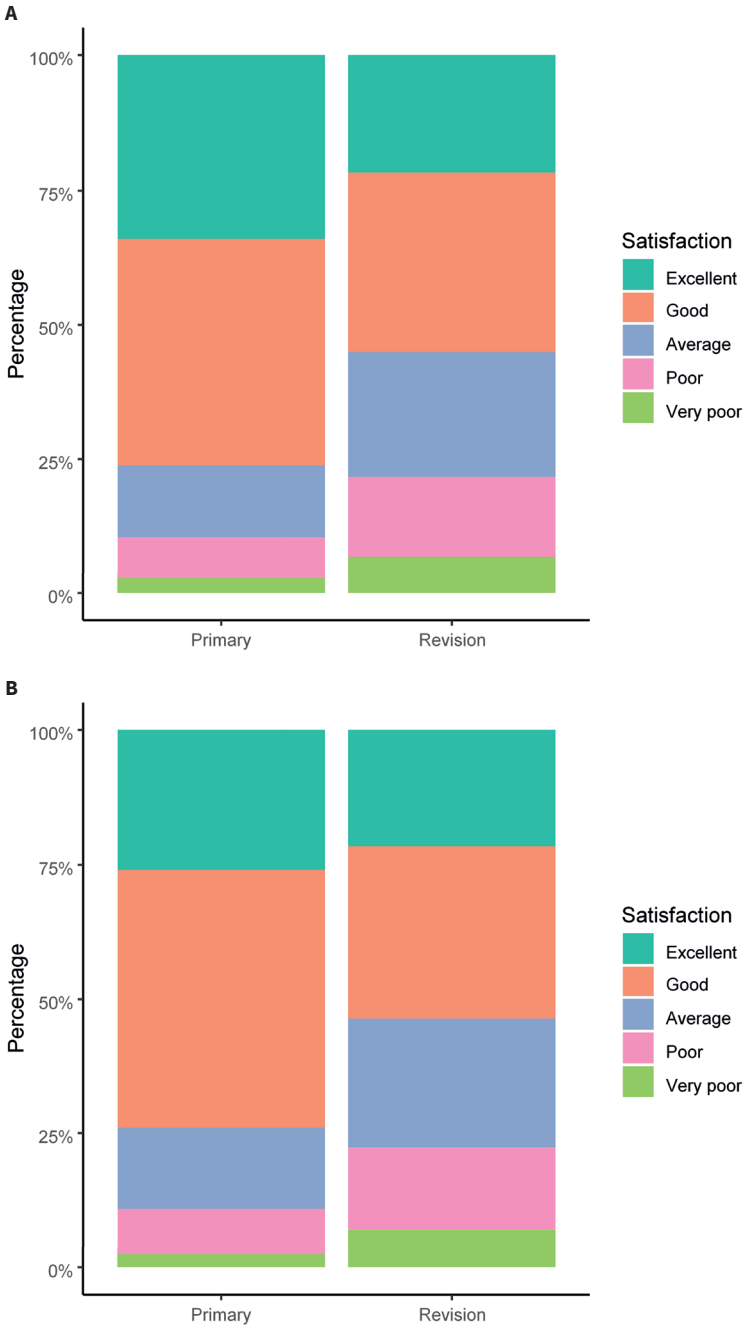

Figure 2. Outcome in satisfaction with the treatment result measured at 6 months follow up in both groups, before matching (A) and after matching (B)
*Before matching: n = 898 for primary patients and n = 129 for recalcitrant patients
*After matching: n = 127 for primary patients and n = 125 for recalcitrant patients

The overall complication rate did not differ between primary and recalcitrant patients (3.4% vs 3.0%, respectively, p=0.963). After matching, 5.5% of primary patients had complications and 3.1% of recalcitrant patients (p=0.538). Most of the complications were wound infections treated with antibiotics, except for 16 primary patients with wound dehiscence.

Figure 2 presents the patient satisfaction with the outcome of the treatment six months after surgery, with almost similar results before and after matching. Primary patients were more satisfied compared to recalcitrant patients (excellent/good (before matching): 76% vs 55%, p=<0.001). Additionally, 86% of primary patients would have opted for CTR again, compared to 82% of recalcitrant patients.

When comparing the subgroups of recurrent and persistent symptoms within the recalcitrant group, we found no differences in BCTQ scores at six months and improvement in BCTQ scores between patients of both subgroups (Table 2).

Table 2. Subgroup analysis of recurrent versus persistent CTS

Outcome	Recurrent (n = 65)	Persistent (n = 67)	*P value*
	Score (SD)		
BCTQ total (6mo)	1.94 (0.6)	1.93 (0.7)	0.902
FSS (6mo)	1.92 (0.6)	1.94 (0.7)	0.885
SSS (6mo)	1.98 (0.6)	1.92 (0.7)	0.626
BCTQ difference	0.87 (0.7)	0.94 (0.7)	0.570
FSS difference	0.76 (0.8)	0.77 (0.7)	0.927
SSS difference	0.95 (0.8)	1.10 (0.8)	0.288

DISCUSSION

This study shows that the outcome after revision CTR is worse compared to primary CTR, both uncorrected and corrected for confounding using propensity score matching. The BCTQ total score at six months was better in primary patients (1.55±0.58) than in recalcitrant patients (1.94±0.73, p=<0.001). The difference between the groups of 0.39 points can be partly explained by differences in baseline symptom severity, functional status and patients demographics since matching patients with similar baseline characteristics reduces the difference in BCTQ total score at six months to 0.27 points (1.65 in primary patients and 1.92 in recalcitrant patients). Although differences between the groups in BCTQ total score seem small, primary patients were more satisfied with the outcome after CTR compared to recalcitrant patients. The overall complication rate between the groups was not different. When comparing the subgroups of recurrent and persistent symptoms

within the recalcitrant group, we found no differences in BCTQ scores at six months and improvement in BCTQ scores between patients of both subgroups.

To our knowledge, this study is the first to directly compare the outcome of primary and revision CTR. Previous research has suggested that the outcome after primary CTR might be better than the outcome after revision CTR[13, 14] and this study confirms that. Furthermore, the postoperative BCTQ scores of patients that underwent primary CTR in our study are consistent with a previous study by Kleermaeker et al. [13]. While our patients had postoperative scores of 1.55±0.58 for both the FSS and SSS subscales, they reported postoperative scores at six months of 1.54±0.65 on the FSS subscale and 1.54±0.66 on the SSS subscale. In addition, the mean postoperative BCTQ-scores of our recalcitrant group were in line with a previous study by Cobb et al.[14] Our recalcitrant patients had postoperative scores of 1.93±0.76 on the FSS subscale and 1.95±0.77 on the SSS subscale, and they reported a score of 1.95±0.90 on the FSS subscale and 1.92±0.82 on the SSS subscale; however, it is not clear at what time after surgery this was measured.

The difference in BCTQ-scores between the primary and revision group declined after propensity score matching. This means matched patients with similar baseline severity and demographics also have more similar outcomes compared to the general (unmatched) study population. Therefore, we conclude that the variables on which we matched the patients might be associated with the postoperative outcome. This is in line with previous research that preoperative symptom severity, functional status, comorbidities, and work-related factors are predictors of the outcome [17, 18, 38, 39]. Nevertheless, the difference between the groups remains significant, indicating that other factors contribute to this difference. A reasons might be that recalcitrant patients have already had previous surgery, followed by persistence of symptoms or redevelopment of symptoms. Moreover, recalcitrant CTS has multiple etiologies, such as an incomplete release, a misdiagnosis, or perineural fibrosis [12, 40]. While these factors could make revision surgery more difficult and are important to keep in mind, they have not yet been investigated as predictors of the outcome after revision surgery and we were unable to include these factors in this study because these factors do not play a role in primary patients.

Furthermore, psychological factors like depression, pain catastrophizing and patients' expectations of treatment have been proven to affect the outcome after surgery[41] and could, therefore, influence the difference in self-reported effectiveness between the two groups in our study[38, 42-45]. We did not include these factors in this study because we did not have enough data available on this. However, it would be interesting to analyse this in further research.

A clinically important improvement on the BCTQ total score was reached in 59% of unmatched primary patients and 50% of unmatched recalcitrant patients. Before matching, 10% of recalcitrant patients had a BCTQ total score of 1.00 at six months (i.e. no complaints), compared to 18% of primary patients. Previous studies by Cobb et al.[14], Beck

et al.[15], and Jones et al.[12] reported complete relief of symptoms in recalcitrant patients in 34%, 54%, and 57% of patients respectively. Kleermaeker et al.[13] noted a complete relief of symptoms in 57.5% of primary patients. The discrepancy in rates between these studies and our study might be due to the definition of complete relief; they used unspecified definitions, while we used a strict BCTQ total score of 1.00. Hence, looking into patients without any improvement might be more generalizable. In our study, 5.5% of unmatched primary patients and 11.6% of unmatched recalcitrant patients did not notice any improvement after surgery. These rates are lower than those reported in previous studies[12, 14, 15]. It is plausible that the higher percentage of recalcitrant patients without any improvement is related to the etiologies of recalcitrant CTS, as mentioned earlier. Regrettably, we did not have data available to determine whether patients without any improvement turned out to have an alternative diagnosis.

Considering postoperative satisfaction, a higher percentage of primary patients (excellent/good: 76%) were satisfied with the outcome of CTR compared to recalcitrant patients (55%). This difference seems higher compared to the differences in BCTQ outcome rates between the groups. This suggests that primary patients may be more likely to be satisfied with similar results than recalcitrant patients. Previous studies have already suggested that psychological factors like depression, anxiety and coping mechanisms influence perceived symptom severity and adaptation to objective dysfunction and therefore satisfaction after surgery[42, 44]. In addition, Kadzielski et al. [44] stated that patient satisfaction is best predicted by the fulfilment of expectations. Thus, it would be interesting for future research to focus on differences in psychological factors between primary and revision CTR.

Strengths of this study include the relatively large sample size and the broad range of prospectively gathered questionnaires used as our outcome measures. Our study also has several limitations. First, some of the comorbidities and concomitant procedures were collected retrospectively from the medical records; therefore, we might be missing out on information that was not well documented by the physician. Second, a proportion of the recalcitrant patients (23%) had missing values for BMI, smoking and alcohol use. We did not include these variables in the matching procedure since this would decrease the number of patients and since previous studies showed that variables are not related to the clinical outcome.[15, 17, 28] As a sensitivity analysis, we did perform an addition analysis (not reported) where we also matched on these variables, and found similar results in the BCTQ-total score at six months: better outcome in primary patients (1.65±0.62) than in recalcitrant patients (1.86±0.69, p=0.031). Third, exact data on additional procedures performed in the revision group was not available in a standardized format. Although an additional hypothenar fat pad flap procedure seems successful[11, 46], the study by Pace et al.[47] showed no difference in self-reported symptom severity or functional scores between recalcitrant patients undergoing CTR with or without a fat pad transposition. Fourth, we

did not evaluate the surgeon's experience, whereas this may affect surgical outcome[48]. But, it is unlikely that this influenced the outcome of CTR between the groups in our study, considering patients of both groups were treated by the same surgeons in the same clinics[17, 49]. Fifth, although we tried to reduce differences in baseline characteristics between the groups using propensity score matching, we were unable to correct for residual confounding.

In conclusion, our work confirmed that the outcome after revision CTR is worse compared to the outcome after primary CTR. The results of our propensity score-matched analysis indicate that a worse baseline symptom severity, a worse functional status and preoperative demographics (age, sex, workload, dominant side treated, comorbidities, and the presence of CTS on both sides) may play a role in this difference in outcomes. These results can serve as a design for more accurate counselling of patients prior to surgery and provides new insights for future research. Future research should focus on the influence of pathophysiological changes after primary surgery on the outcome of revision CTR and on the investigation of differences in psychological factors between primary and recalcitrant patients undergoing CTR.

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8 | Recurrent and persistent carpal tunnel syndrome: predicting clinical outcome of revision surgery

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ABSTRACT

Objective

The aim of this study was to evaluate the self-reported outcome of revision surgery in patients with recurrent and persistent carpal tunnel syndrome(CTS) and to identify predictors of clinical outcome of revision surgery.

Methods

A total of 114 hands in 112 patients were surgically treated for recurrent and persistent CTS in 1 of 10 specialized hand clinics. As part of routine care, patients were asked to complete online questionnaires regarding demographic data, comorbidities and clinical severity measures. Symptom severity scale(SSS) and function status scale(FSS) were measured with the Boston Carpal Tunnel Questionnaire (BCTQ) at intake and at 6 months postoperatively to evaluate the clinical outcome. Using multivariable regression models, we identified factors predictive of the outcome as measured by the BCTQ FSS, SSS and total score at 6 months.

Results

Revision surgery significantly improved symptoms and function. Longer total duration of symptoms, a higher BCTQ total score at intake and co-diagnosis of Complex Regional Pain Syndrome (CRPS) were associated with worse outcome after revision surgery at 6 months postoperatively. Respectively 33%, 23% and 30% of the variance in outcome measured by FSS, SSS and BCTQ total score could be explained by our multivariable regression models. Although patients with higher BCTQ score at intake have worse outcome, they generally have most improvement of symptoms and function.

Conclusions

This study identified total duration of symptoms, BCTQ total score at intake and co-diagnosis of CPRS as predictors of clinical outcome and confirmed that revision surgery significantly improves self –reported symptoms and function in patients with recurrent and persistent CTS. Patients with more severe CTS symptoms have greater improvement in symptoms at 6 months postoperatively as compared to patients with less severe CTS, but 80% of our patients still had residual symptoms 6 months postoperatively. These results can be used to inform both patient and surgeon to manage expectations on improvement of symptoms.

Key words: Carpal tunnel syndrome, persistent, recurrent, revision surgery, prediction, Boston carpal tunnel questionnaire.

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy of the hand with a prevalence of approximately 5%. [1,8,19,23] Despite the availability of conservative treatment options, surgical decompression of the median nerve is often needed. Consequently, carpal tunnel release (CTR) is the most frequently performed surgical procedure of the hand and is considered generally very successful.

Despite the well-reported success of CTR in most patients,[7] the reported incidence of patients who remain symptomatic after primary CTR is ranging between 1% and 31%.[1,4,16,19,21] Five to 10% of the patients with recurrent and persistent symptoms require revision surgery.[19,21,23]

The outcome of revision surgery for recurrent and persistent CTS is less successful as compared to the outcome of primary surgery; the systematic review and meta-analysis of Soltani et al.[21] reports no improvement of symptoms after repeated decompression with neurolysis in up to 47% and after flap surgery in up to 37%. Furthermore, patients who do have improvement often have residual symptoms following revision surgery.[2,3,23]

In order to identify which patients are more likely to have residual symptoms, individual factors that can predict the outcome are needed, such as average preoperative pain, taking pain medication and workers compensation status. [24] While these factors can predict postoperative pain in patients with recurrent and persistent CTS, no predictors of clinical severity as measured by the Boston Carpal Tunnel Questionnaire (BCTQ) are known. These predictors can be used to inform both surgeon and patient to manage their expectations, which is important because fulfillment of expectations is associated with patient satisfaction after revision surgery for CTS. [12]

Therefore, the goal of this study is to analyze the self-reported clinical outcome of revision surgery for CTS and to identify which individual factors are predictive of the clinical outcome. Furthermore, we will create a prediction model using different baseline factors. Our results can be used to inform the patient and surgeon about the outcome based on these individual factors.

METHODS

Study population

We identified patients with recurrent and persistent CTS who underwent revision surgery by 1 of 22 European board certified hand surgeons between January 2011 and Januari 2018 at 1 of 10 specialized hand clinics of Xpert Clinic in the Netherlands. Patients were asked as part of routine care to complete online questionnaires in our web-based surgical outcome registration at baseline and at 3 and 6 months postoperatively. All patients of 18 years or

older who had at least 1 prior operation for CTS were included in this study. Furthermore, patients must have filled out the Boston Carpal Tunnel Questionnaire at baseline and at 6 months after surgery. Patients with comorbidities and concomitant surgeries were not excluded because these factors may also be predictive of clinical outcome. Approval for this study was obtained from the local Institutional Review Board and all patients gave written informed consent.

Treatment

Preoperative workup prior to decision for surgery was similar for all clinics. It consisted of history taking and physical examination by one of the surgeons, who diagnosed CTS based on symptoms and examination findings, according to the current Dutch guideline.[17] Although some of the patients had undergone nerve conduction studies or an ultrasound, diagnosis of CTS was not based on these findings as these can be abnormal after CTR, independently of clinical signs of CTS.[10] Then, the decision to perform surgery was based on whether there were typical clinical signs of CTS, such as tingling and numbness, whether patients were referred or self-operated and whether the patient wanted surgery. All included patients underwent an open CTR on the previously operated hand. This was achieved by repeated decompression, with or without neurolysis, partial synovectomy or a form of flap surgery. Judgment of the surgeons to use a specific technique was based on knowledge and expertise. In general, partial synovectomy was performed in patients with signs of flexor synovitis, neurolysis was performed when the median nerve had adhesions to the surrounding tissue, and flap surgery was performed in patients with extensive perineural fibrosis. The skin was incised with a volar incision in line with the fourth ray which in most patients was extended proximally, with a short tranversal break at the wrist crease to prevent longitudinal contraction by scar formation. Standard postoperative care was provided for all patients, consisting of 3 days of bandages and a sling around the operated hand. During the first 3 days, the hand therapist started standardized handtherapy beginning with tendon gliding exercises. Subsequently, exercises for the range of motion of the wrist and nerve gliding were started. Two weeks postoperatively patients were seen to monitor progress and remove sutures. Then, treatment against scar formation was started and exercises were intensified if necessary.

MEASUREMENTS

Baseline characteristics

The following demographic data were collected at intake: age, sex, BMI, hand dominance, operated hand, recurrent or persistent symptoms, duration of symptoms, time between carpal tunnel releases, number of prior carpal tunnel releases, comorbidities, workload,

smoking and alcohol use. Whether symptoms were recurrent or persistent was determined from the medical records. Recurrent CTS has previously been defined as the recurrence of symptoms after an undefined symptom-free interval following surgery.[11,22,24] As this definition does not clarify the duration of this interval, we held on to a minimal symptom-free period of 3 months after surgery. When symptoms persisted directly after surgery or came back within 3 months after surgery, CTS was classified as persistent. Since physical examination was not recorded in a standardized way, it was not possible to present these findings.

The following comorbidities were collected: diabetes mellitus, rheumatic arthritis, polymyalgia rheumatica, gout, fibromyalgia, Sjögren syndrome, Trigger fingers, Dupuytren's disease, cubital tunnel syndrome, radial tunnel syndrome, Complex Regional Pain Syndrome (CRPS), first carpometacarpal osteoarthritis (CMC1 OA), De Quervain's disease and tendinitis. Rheumatic arthritis, polymyalgia rheumatica, gout, fibromyalgia and Sjögren syndrome are grouped under "rheumatic diseases". Cubital tunnel syndrome, ulnar nerve entrapment and radial tunnel syndrome are grouped under "other nerve compressions". Comorbidities were diagnosed by a physician, based on the medical history, physical examination, radiographic imaging or electrodiagnostic testing. In case of CRPS, patients were already diagnosed when they presented at Xpert Clinic. When specific comorbidities were present in less than 5 patients, then these comorbidities were not used in the multivariable regression models.

Peri-operative data were also collected: surgical procedure (repeated decompression only, or with neurolysis and/or partial synovectomy, flap surgery), concomitant procedures and complications. Concomitant procedures were used in our multivariable model, defined as either performed or not.

Primary outcome measurement: Boston Carpal Tunnel Questionnaire

The Boston Carpal Tunnel Questionnaire (BCTQ, Dutch Language Version[20], BCTQ; 1= no complaints, 5= maximum complaints possible) was used to assess clinical severity at baseline, 3 months and 6 months postoperatively. BCTQ is comprised of 2 domains, the Symptom Severity Scale(SSS) and Functional Status Scale(FSS), consisting of 11 and 8 items respectively. First, the clinical outcome of revision surgery at 6 months postoperatively was analyzed. We compared mean scores for FSS, SSS and BCTQ total score and analyzed outcomes for subgroups based on FSS, SSS and BCTQ total score at intake, by dividing the patients into 4 groups: patients with preoperative BCTQ scores less than or equal to 2.0, between 2.0 and 3.0, between 3.0 and 4.0 and greater than or equal to 4.0. Secondly, we analyzed baseline factors that could potentially predict the clinical outcome of revision surgery. Finally, satisfaction at 6 months postoperatively and the relation between satisfaction and clinical improvement was analyzed.

Complications

Complications were registered during the 6 months' period after surgery. The following complications were recorded if present: Infection treated with antibiotics, wound dehiscence, postoperative bleeding and injury to the median nerve and palmar cutaneous branch. Complications were used as outcome measure but were not used in the multivariable models, because only four patients had a complication.

Statistical analysis

Due to non-response, a proportion of the included patients had missing values for the following variables at baseline: BMI(27%), smoking status(27%), alcohol usage(27%) and time between last and previous CTR(3%). Non-response for outcome measures was 5% for BCTQ scores at 3 months and 4% for satisfaction.

We perfomed a non-responder analysis between patients with and without BCTQ scores at 6 months postoperatively to check for selection bias due to exclusion and because of the amount of missing values (Supplementary Table 1). Baseline variables and BCTQ scores at 3 months between patients with and without BCTQ scores at 6 months postoperatively were compared by using Chi-square tests for categorical variables and unpaired T-tests for continuous variables. No significant differences were found, hence we concluded that missing data were independent of observable and unobservable variables.

To identify individual baseline factors that are associated with the clinical outcome of revision surgery for CTS, defined as the FSS score, SSS score and BCTQ total score at 6 months postoperatively, we performed multivariable regression analyses with the following variables: age, sex, duration of symptoms, number of previous CTR's(1 or >1), type of symptoms(recurrent or persistent), workload, BCTQ total score, DM, Rheumatic diseases, CRPS, trigger finger, CMC1 OA and other nerve compression syndromes. Then, to develop prediction models for the FSS score, SSS score and BCTQ total score at 6 months postoperatively, we used the same baseline variables in backward stepwise multivariable regression analyses for variable selection. Subsequently, the residual factors were used in multivariable regression analysis to determine the R^2 of each model, a measure of the variance in outcome that can be explained by the model.

Finally, to assess whether patients with more improvement in BCTQ total score at 6 months had higher probability of rating their satisfaction at 6 months as good or excellent, we used a logistic regression model. Satisfaction was divided in good/excellent and moderate/fair/poor. Improvement in BCTQ total score was calculated by substracting the BCTQ total score at 6 months from the score at intake.

P values ≤ 0.05 were considered statistically significant. The statistical software package Rstudio(version 1.0.143) was used for analysis and processing of the data.

RESULTS

Study population

After exclusion of the patients with missing values for baseline and 6 months BCTQ scores, 112 patients remained with revision surgery in 114 hands (Figure 1). The included patients consisted of 28 men and 84 women with a mean age of 55.5 years. Recurrent symptoms were seen in 49 hands and persistent in 65 hands. All baseline chararacteristics are showed in Table 1.

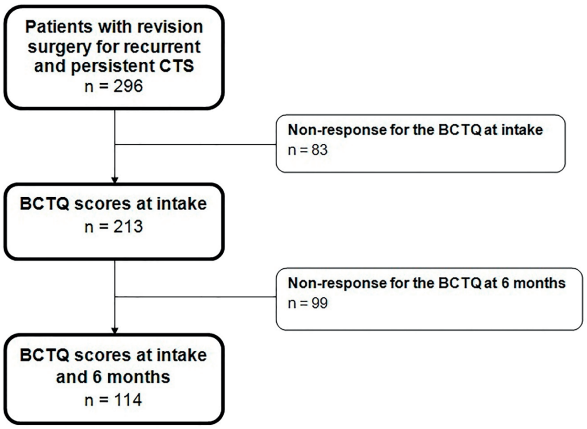

Figure 1. Study flowchart

Surgical outcome

The mean FSS, SSS and BCTQ total score at 6 months postoperatively are 1.92, 1.91 and 1.91, respectively, and all are significantly improved($p<.0001$) as compared to baseline. The mean improvement of FSS, SSS and BCTQ total score and their distributions at intake and 6 months postoperatively can be seen in Figure 2A-C.

Improvement of the BCTQ total score at 6 months after surgery was seen in 104 hands (91%) with a mean of 1.05 points (±0.61). No improvement or detoriation on the BCTQ total score at 6 months was seen in 10 hands (9%) with a mean increase of 0.28 points (±0.22). We also assessed the improvement of BCTQ scores for subgroups of patients grouped on their score at intake. Figure 3A-C shows that patients with BCTQ scores at intake ≥4.0 have, on average, most improvement over 6 months, followed by the subgroup with BCTQ scores between 3.0 and 4.0, then the subgroup with BCTQ scores between 2.0 and 3.0 and lastly the subgroup with BCTQ scores ≤2.0. Of the 10 hands with no improvement or detoriation, 2 were in the subgroup of 8 hands with BCTQ total score at intake ≤2.0, while the other 8 hands with no improvement or detoriation had BCTQ total scores at intake between 2.0 and 4.0. All of the 6 hands with BCTQ total scores at intake ≥ 4.0 had improvement. Furthermore, most patients have residual symptoms, despite of their BCTQ score at intake.

Table 1. Baseline characteristics of the study population (n=114).

Baseline Characteristics		Study population (n=114)
Categorical Variables		***n (%)***
Sex	**Female**	86 (75)
Operated hand	**Right**	68 (59)
Smoking		18 (21)*
Alcohol usage		27 (32)*
Recurrent symptoms		49 (43)
> 1 previous CTR		11 (10)
Comorbidities	**Diabetes mellitus**	10 (9)
	Rheumatic diseases	22 (19)
	Trigger finger	25 (22)
	CMC1 OA	10 (9)
	De Quervain tenosynovitis	3 (3)
	Dupuytren's disease	2 (2)
	CRPS	6 (5)
	Tendinitis of the wrist	3 (3)
	Other nerve compressions	9 (8)
Concomitant procedures	**Trigger finger release**	10 (9)
	Excision of (ganglion) cyst	2 (2)
	Camitz opponensplasty	1 (1)
Workload	**No work**	46 (40)
	Light physical work	27 (24)
	Moderate physical work	26 (23)
	Heavy physical work	15 (13)
Dominance	**Left**	9 (8)
	Right	100 (88)
	Co-dominant	5 (4)
Continuous Variables		***Mean ± SD***
Age (years)		55.5 ± 13.1
BMI (kg/m^2)		27.0 ± 4.7 *
BCTQ (1-5)	**Symptom severity scale***	2.99 ± 0.6
	Functional severity scale*	2.71 ± 0.7
	Total*	2.85 ± 0.6
Time between previous and last CTR		54.2 ± 70.4**
Duration of complaints in months		26.7 ± 37.2

***n=81**

****n=111**

BCTQ = Boston Carpal Tunnel Questionnaire; CMC1 OA = first carpometacarpal osteoarthritis; CRPS = Complex Regional Pain Syndrome; CTR = carpal tunnel release; FSS = functional status scale; SSS = symptom severity scale.

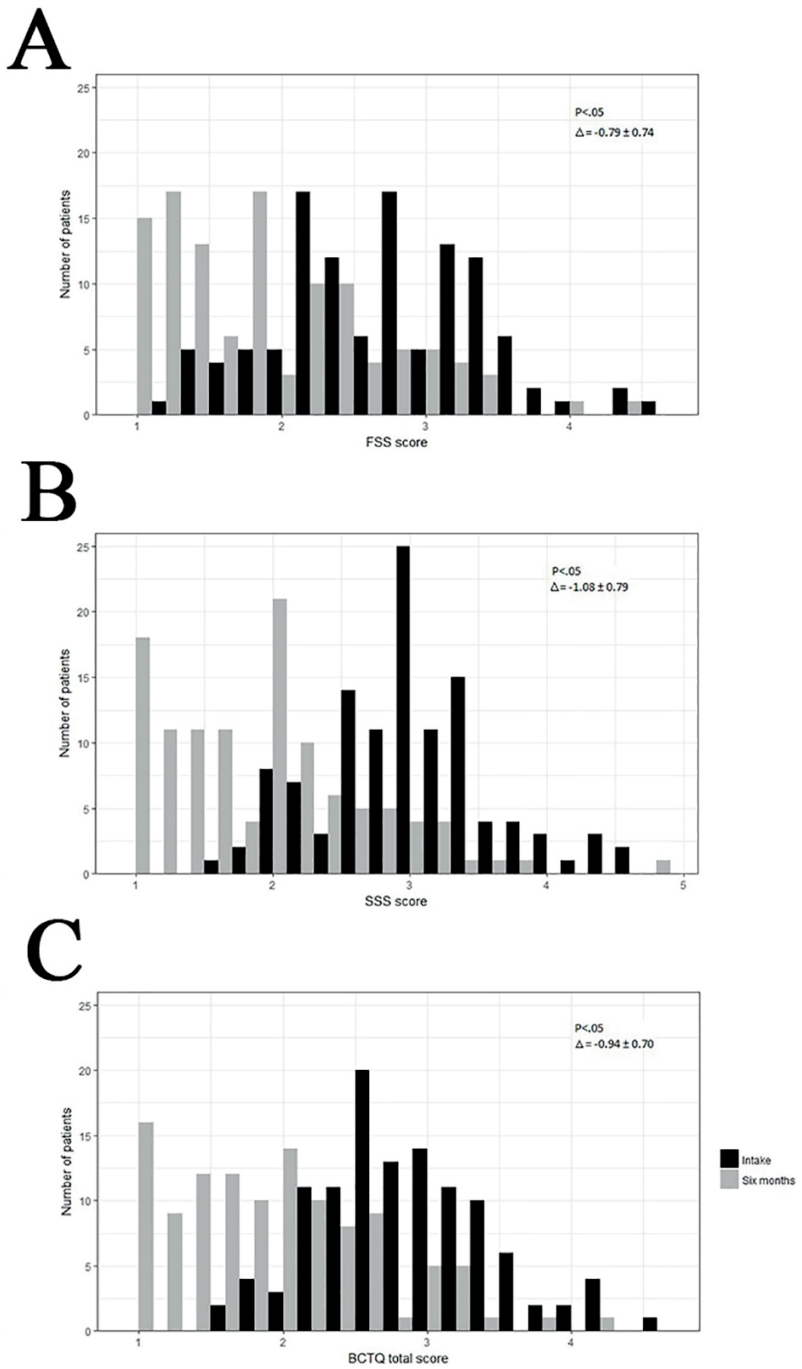

Figure 2. A Distributions of FSS, **B** SSS, and **C** BCTQ total score at intake and 6 months postoperatively, with in the right upper corner the P-value of t-test and deltas for the mean differences between pre- and postoperative scores with corresponding standard deviation.

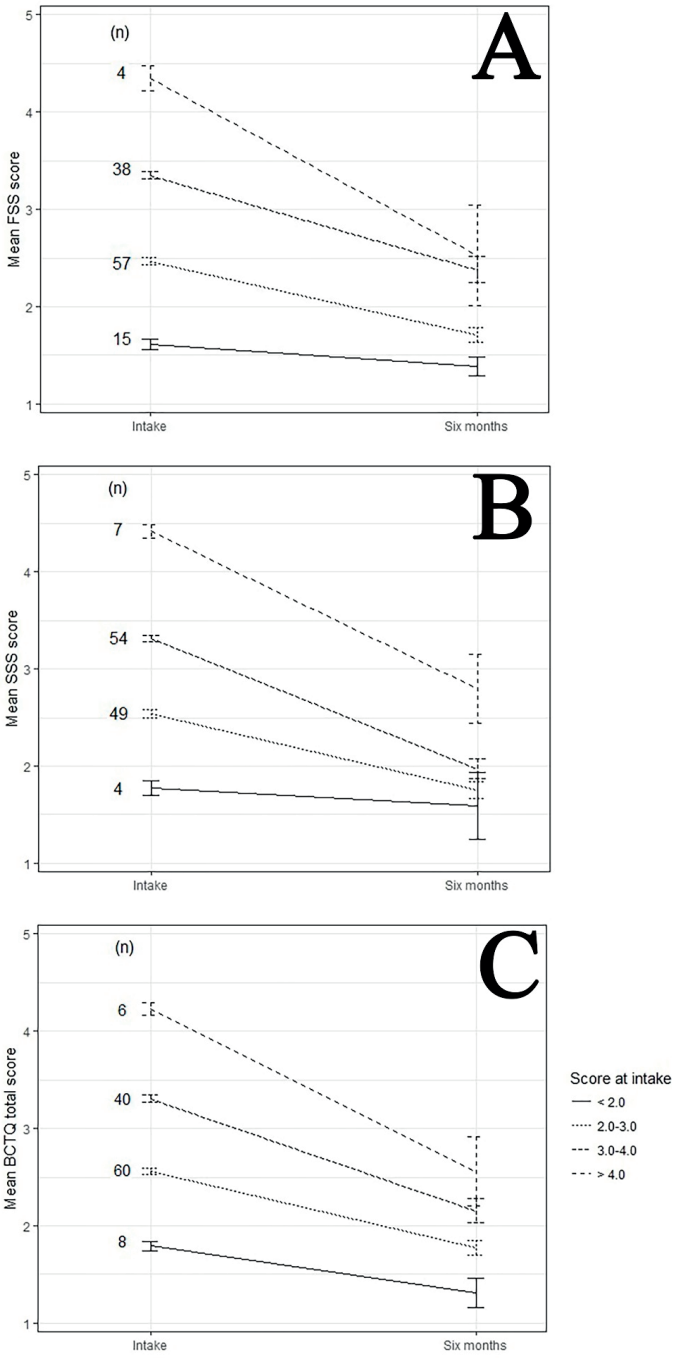

Figure 3. A Postoperative course of the FSS, **B** SSS, and **C** BCTQ total score of subgroups of patients grouped on their score at intake. Error bars represent the standard error of the mean. The numbers (n) at intake are the number of included patients per subgroup.

Repeated decompression only was performed in 43 hands (37%), while also neurolysis and partial synovectomy was performed in 57 (50%) and 27 hands (24%), respectively. Flap surgery was performed in 4 hands (4%). Hypothenar fat pad flap was perfomed in 3 patients and palmaris longus interposition in 1 patient. Complications were registered in 4 patients (4%). They all had a mild wound infection which was succesfully treated with antibiotics. Despite of the complication, all had improvement of BCTQ scores.

Predictors

Multivariable regression analysis showed that more severe BCTQ total score at intake and co-diagnosis of CRPS are significantly associated with a worse FSS, SSS and BCTQ total score at 6 months postoperatively . In addition, longer total duration of symptoms is significantly associated with worse SSS and BCTQ total score at 6 months postoperatively. We found the same variables to be significant in the prediction models for FSS, SSS and BCTQ total score at 6 months as the multivariable regression analyses without backwards stepwise selection (Table 2). More than 1 previous CTR and co-diagnosis of DM and other nerve compressions were also included in our prediction models but were not significantly associated with the outcome.The multivariable prediction models could explain 33%, 23% and 30% of the variance in outcome as measured by the FSS, SSS and BCTQ total score, respectively, at 6 months.

Table 2. Multivariable regression analysis after stepwise backward selection with beta-coefficients representing the relation between baseline variables and surgical outcome, as measured by BCTQ scores at 6 months postoperatively.

Baseline Variables	Six months after surgery		
	Δ SSS-score β (SE)	Δ FSS-score β (SE)	Δ Total BCTQ – score β (SE)
R^2 (% explained variance) for the complete model	**23%**	**33%**	**30%**
Constant	0.675* (0.312)	0.469 (0.294)	0.595* (0.279)
Total duration of symptoms in months	0.0047** (0.0017)	0.0027 (0.0016)	0.0035* (0.0015)
BCTQ total score	0.400*** (0.108)	0.453*** (0.102)	0.406*** (0.257)
Previous CTR > 1	-0.333 (0.207)		
Co-diagnosis of CRPS	0.600* (0.286)	1.039*** (0.272)	0.829** (0.26)
Co-diagnosis of Diabetes Mellitus	-0.324 (0.220)		
Co-diagnosis of other nerve compressions		0.368 (0.218)	0.324 (0.206)

***Association found to be significant at a p-level <0.05.**
****Association found to be significant at a p-level <0.01.**
****Association found to be significant at a p-level <0.001.**
BCTQ = Boston Carpal Tunnel Questionnaire; CRPS = Complex Regional Pain Syndrome; CTR = carpal tunnel release; FSS = functional status scale; SSS = symptom severity scale

Satisfaction

Satisfaction was rated for 110 hands. Twenty three (21%) rated the outcome of revision surgery as excellent, 38 (35%) rated the result as good, 26 (24%) rated the result as moderate, 16 (15%) rated the result as fair and 7 (6%) rated their results as poor. Logistic regression analysis showed that greater improvement of BCTQ total score has higher odds(p=0.02) of patients rating their satisfaction as good or excellent (Figure 4).

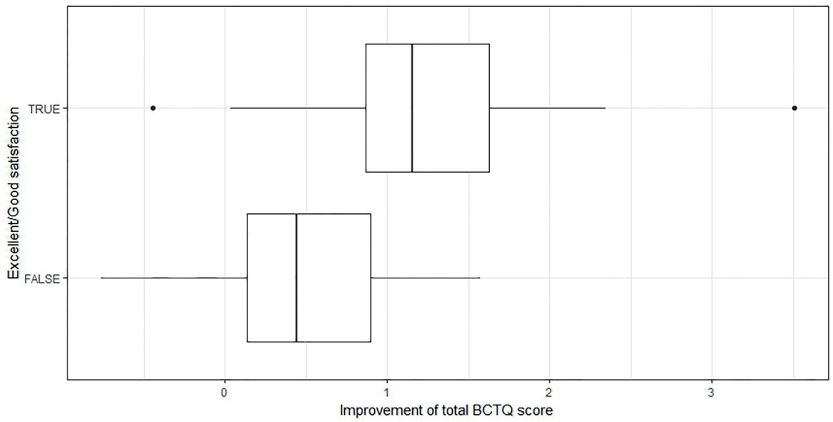

Figure 4. Boxplot showing the distribution of improvement in patients with excellent/good satisfaction (TRUE) and patients with moderate/fair/poor satisfaction (FALSE).

DISCUSSION

This study confirms that revision surgery for CTS is on average an effective treatment for patients with recurrent and persistent symptoms. Patients with more severe symptoms and functional status at intake, as defined by a high BCTQ total score, have more improvement as compared to patients with lower BCTQ score at intake. However, these patients also have more residual symptoms after revision surgery. This is in line with our finding that higher BCTQ total score at intake is predictive of worse outcome of revision surgery. In other words, although patients with high BCTQ scores have most improvement after 6 months, they still have worse outcome and more residual symptoms as compared to patients with lower BCTQ scores, because their scores at intake were higher. Our study also shows that longer duration of symptoms and co-diagnosis of CRPS are predictive of a worse clinical outcome, as measured by FSS, SSS and BCTQ total score at 6 months postoperatively. Furthermore, the majority of variation in the effect of revision surgery on the clinical outcome could not be explained, as the variables used in our multivariable models could explain only 23-33% of variation.

Surgical treatment of recurrent and persistent CTS has been shown to be effective in reducing symptoms.[3,23,24] Our postoperative mean FSS and SSS scores are comparable to those of Cobb et al.,[3] who found 1.95 and 1.92 respectively. In our group, 91% had improvement in BCTQ total score after 6 months. However, this is the absolute number of patients with improvement. When taking into account the minimal clinically important difference for the BCTQ scores,[14] clinically important improvement was seen in 52% for FSS score and 53% for SSS and BCTQ total score. Eleven patients had a BCTQ total score of 1.00 after 6 months, meaning only 11% had complete relief of symptoms. This is lower as compared to previous literature of Jones et al.,[11] Beck et al.[2] and Cobb et al.,[3] who reported complete relief in respectively 57%, 54% and 34% of all patients. A possible explanation might be how improvement was measured. Jones et al. and Beck et al. categorized their patients' symptoms as completely relieved, improved or unchanged, while the BCTQ score might record minor residual symptoms in patients which would classify their symptoms as completely relieved. Nevertheless, if we would raise the BCTQ total score to 1.5, as patients with minor residual symptoms might report their symptoms as completely relieved, we would reach 32% with complete relief which is still less than found by Jones et al. and Beck et al. but comparable to Cobb et al. Another reason why less patients had complete relief could be explained by performing almost exclusively repeated decompression instead of flap surgery, which seems to have higher success rate than repeated decompression.[21] Since 11% of our patients had complete relief and 9% had no improvement, 80% of our patients with improvement had residual symptoms, which are often present after revision surgery.[2,3,23] The patient should be informed about this before performing surgery, as expectations may not be fulfilled otherwise. Lastly, we found that 25% (2 out of 8) of the hands with BCTQ score ≤2.0 showed no improvement or detoriation, as compared to only 8% (8 out of 106 hands) in the rest of the population. This suggests that surgery should be carefully considered in patients with low baseline BCTQ scores.

Only few studies have assessed predictors of the outcome of revision surgery and none of them used BCTQ scores as endpoint. The study of Zieske et al.[24] found that more than 1 prior CTR and persistent symptoms had higher odds of worse postoperative pain and found preoperative average pain, taking pain medication and workers'compensation status as significant predictors for postoperative pain. Although we were not able to analyse pain medication and compensation status, we did not find an association between worse outcome and more than 1 prior CTR or persistent symptoms. This difference might be explained by the fact that BCTQ does assess more than only pain, which was the outcome measure of Zieske et al. While they found average preoperative pain to be a predictor of postoperative pain, we found preoperative FSS score to be a predictor of postoperative BCTQ score. It may be that some measure of preoperative severity can be predictive of the postoperative outcome. Furthermore, Zieske et al. did not find comorbidities with higher odds of worse average postoperative pain, whereas we found co-diagnosis of CRPS to

be significant associated with worse BCTQ scores after 6 months. A possible explanation is that the BCTQ score is affected by other comorbidities that affect the hand, therefore the presence of these comorbidities might not be predictive for the outcome of revision surgery for CTS. Nevertheless, first carpometacarpal osteoarthritis and trigger fingers also affect the hand and can mistakenly be taken for CTS, but those were not predictors of clinical outcome in our study. Other studies regarding factors predictive of outcome have reported the following: intraneural scarring, severe preoperative sensory deficits[5] ulnar nerve symptoms and normal electrodiagnostic testing[3] for worse outcome, whereas relief after injection with cortisone in combination with components of physical exam findings could predict surgical success. [2]

Approximately 77%-67% of the variance could not be explained by our prediction models. Although this is similar to the study of Zieske et al, a large part remains unexplained by our model meaning that other variables which we could not examine may very likely play a role in prediction of the outcome of revision surgery. For example, workers` compensation has been shown to be a predictor,[5,24] but was not included in our questionnaires. Furthermore, we were not able to analyze the psychological factors like depression, pain catastrophization and patients' expectations of their treatment, while those factors could be of importance in evaluating treatment effect on postoperative patient reported outcomes regarding the upper extremity.[12,13,15,18]

Our study has several strengths and limitations. The strengths are the prospectively gathered data and the relatively large sample size for revision surgery for recurrent and persistent CTS, due to our multi-center data gathering. As surgery was performed in multiple centers by different surgeons, there might have been an effect of specific surgeons or practice sites. Evers et al.[6] showed that outcome of CTR was independent of surgeon volume in the same hand clinics. Also, when comparing the outcome between centers with 10 or more revision surgeries (n=6, mean number of revision surgeries = 16.3) and those with less than 10 (n=4, mean number of revision surgeries=4.0), we found no significant differences (p=0.46). Limitations were as followed: due to the voluntary basis of our online questionnaire, we had to exclude a proportion of our patients because of missing BCTQ scores at 6 months postoperatively. By excluding those patients, we might not have a valid representation of our CTS cohort. However, we performed a non-responder analysis between patients with and without BCTQ scores at 6 months postoperatively, which showed no significant differences for baseline demographics and BCTQ scores at 3 months. Therefore, we assume we have a valid representation of our CTS cohort despite the exclusion of non-responders. We also had missing data on BMI, smoking status and alcohol usage. These variables were not included in the analysis as they have not been shown to be predictors of the clinical outcome of revision carpal tunnel surgery[24] and due to our sample size only a limited number of baseline variables could be analyzed in our multivariable regression analysis. In addition, inclusion of BMI, smoking status and alcohol would have

led to the exclusion of 33 patients resulting in loss of power. The power of our study was sufficient for the analysis we performed, since we included 1 variable for approximately every 9 patients in the analysis.[9] However, the power was insufficient to analyze all of our examined variables. We might have been able to explain more of the variance of our model if we would have had a bigger sample size. Another limitation is that we had to retrieve some data, like some of the comorbidities and concomitant procedures, retrospectively from medical records. Therefore, it is possible that we missed out on information that has not been well documented within the medical records. At last, electrodiagnostic testing and ultrasound was performed in only few patients, mostly elsewhere, therefore we could not analyze the prognostic effect of electrodiagnostic and ultrasound findings on clinical outcome. Cobb et al. showed that those who have abnormal findings on nerve conduction studies before reoperation have significantly better final SSS and FSS scores than those with normal findings, hence including it in our model might have increased the explained variance. Furthermore, electrodiagnostic and ultrasound findings could have contributed to characterization of our population.

Conclusions

In conclusion, this study shows that revision surgery for CTS significantly improves self-reported symptoms and function, especially in patients with more severe CTS. However, a large group of patients remain symptomatic. Furthermore, we found BCTQ total score at intake, total duration of symptoms and co-diagnosis of CRPS to be predictors of the outcome of revision surgery. With these findings, surgeons and patients may be better informed about who benefits less or more from revision surgery and who is more likely to remain symptomatic. However, around one third of variance in outcome could be explained by our multivariable models, therefore future research should aim at studying the predictive value of psychological factors, like mental health and patient expectations, on clinical outcome after revision surgery.

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Supplementary Table 1. Non-responder analysis between patients with and without BCTQ scores at 6 months postoperatively. Patients characteristics at intake and FSS, SSS and BCTQ total score at 3 months postoperatively were compared.

Baseline Characteristics		Non-responder analyses (N=213)		
		Responders at intake and six months (n=114)	Responders at intake and non-responders at six months (n=99)	
Categorical Variables		%	%	**P-value**
Sex	**Female**	75	70	*0.50*
Operated hand	**Right**	59	61	*1*
Smoking		21	16	*0.77*
Alcohol usage		32	37	*0.72*
Workload	**No work**	40	39	*0.70*
	Light physical work	24	19	
	Moderate physical work	23	29	
	Heavy physical work	13	12	
Dominance	**Left**	8	10	*0.76*
	Right	88	87	
	Co-dominant	4	3	
Continuous Variables		**Responders at intake and six months (n=114)**	**Responders at intake and non-responders at six months (n=99)**	
		Mean ± SD	*Mean ± SD*	**P-value**
Age (years)		55.5 ± 13.1	52.1 ± 13.9	*0.08*
BMI (kg/m^2)		27.0 ± 4.7	25.9 ± 4.7	*0.21*
BCTQ (1-5) INTAKE	**Symptom severity scale**	2.99 ± 0.6	2.90 ± 0.69	*0.33*
	Functional severity scale	2.71 ± 0.7	2.56 ± 0.75	*0.13*
	Total	2.85 ± 0.6	2.73 ± 0.64	*0.16*
BCTQ (1-5) THREE MONTHS	**Symptom severity scale**	1.88 ± 0.69	1.81 ± 0.67	*0.60*
	Functional severity scale	1.85 ± 0.64	1.85 ± 0.67	*0.97*
	Total	1.87 ± 0.62	1.83 ± 0.63	*0.78*
Duration of complaints in months		26.7 ± 37.2	26.5 ± 43.9	*0.63*

BCTQ = Boston Carpal Tunnel Questionnaire

9 | Management of recurrent carpal tunnel syndrome: Systematic review and meta-analysis

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ABSTRACT

Purpose

Little comparison between outcomes of surgical techniques for recurrent carpal tunnel syndrome(CTS) has been conducted. This study aims to compare the outcomes of different surgical techniques using the Boston Carpal Tunnel Questionnaire (BCTQ) and the Visual Analog Scale (VAS) for pain through a meta-analysis.

Methods

Studies were assigned to one of the treatment groups neurolysis, autologous fat transfer, hypothenar fat pad, pedicled flap, and the 'other' treatment group based on the intervention. As our primary outcome, we compared the pooled improvement on the BCTQ and VAS pain between treatment groups. As our secondary outcome, pooled post-operative BCTQ and VAS pain values were compared between treatment groups.

Results

From the included studies reporting the BCTQ, five studies were case-series and five were pre-post studies without control groups. For VAS pain, one was a case-series and five were pre-post studies without control groups. Considering our primary outcome, studies reported an average improvement of 1.2 points (95%CI[1.5;0.9]) on the 1-5 Symptoms Severity Scale (SSS) of the BCTQ, 1.9 points (95%CI[1.37;0.79]) on the 1-5 Function Severity Scale (FSS) of the BCTQ, and 3.8 points (95%CI[4.9;2.6]) on the 0-10 VAS pain. We only found significant lesser improvement for the 'other' treatment group compared to the hypothenar fat pad group and the autologous fat transfer group on the SSS. The hypothenar fat pad had the best reported post-operative SSS=1.75 (95%CI=1.24-2.25), FSS=1.55 (95%CI=1.20-1.90), and VAS pain = 1.45 (95%CI=0.83-2.07)).

Conclusions

We found less improvement in the 'other' treatment group compared to the hypothenar fat pad group and the autologous fat transfer group on the SSS. We found that the hypothenar fat pad had the best reported postoperative values in our secondary analysis. However, because of the limited number of the studies, small sample size, and study quality, results should be interpreted with caution.

INTRODUCTION

Carpal tunnel syndrome (CTS) is a common condition and has an estimated prevalence of around 5.8% in women and 0.6% in men in the general population[1]. Carpal tunnel release (CTR) is one of the most common surgical procedures performed on the hand and it has been estimated that, during a lifetime, around 1.9% of men and 4.1% of women undergo a CTR[2].

Although the success rate of CTR is high (around 80%)[3,4], it has been estimated that around 2% to 10% of patients require a CTR revision surgery for recurrent CTS [5-10]. Recurrence of CTS is defined as the reappearance of CTS symptoms after a symptom-free interval of at least three months following CTR[5]. Multiple causes of recurrence of CTS have been described, such as circumferential fibrosis[7,11], reconstitution of the transverse carpal ligament, a nerve injury during the primary intervention[11], or more rare causes such as a tumour in the carpal tunnel[11].

Multiple techniques have been used to treat recurrent CTS including revision decompression[12-14], autologous fat transfer[15], resurfacing of the median nerve with a hypothenar fat pad flap[12,16], or pedicled flaps[17,18], all with variable results[12-18]. However, little comparative research on reported outcomes between different surgical techniques for recurrent CTS has been conducted. So far, only one systematic review has been conducted on this subject by Soltani et al.[19] in 2013 with a total of fourteen included studies. Soltani et al. [19] focused on the success rates of different surgical techniques for recurrent CTS and found that decompression with the use of vascularized flap coverage has a higher success rate over a simple repeated decompression. While the review by Soltani et al.[19] is one of the first to provide an in-depth analysis of the outcomes of different surgical techniques, the different outcome measures of the included studies were categorized into the dichotomous outcome “resolved/improved” or “unchanged/worse”. Although these results give valuable insights into the success rates of different surgical techniques, the different outcome measures used in the included studies are not necessarily directly comparable. This might have influenced the generalizability of their results. In addition, since 2013, multiple studies have been published reporting treatment outcomes on different surgical techniques for the treatment of recurrent CTS[12,16,18,20-25].

By comparing the reported outcomes of specific surgical techniques for recurrent CTS on validated outcome measurements, we aim to provide physicians and patients objective and generalizable results on different treatment options. Therefore, this study aims to establish the current evidence for the various surgical techniques for the treatment of recurrent carpal tunnel surgery by performing a meta-analysis on the treatment outcomes of different surgical techniques for recurrent CTS on comparable and validated patient-reported outcome measurements, such as the Boston Carpal Tunnel Questionnaire(BCTQ)[26] and the Visual Analog Scale (VAS) for pain[27]. The use of these structured and objective

outcome measures in this review provides a more robust and comparable evidence-based guide to the surgical treatment of recurrent CTS.

METHODS

Search strategy

In February 2020, we performed a systematic literature search in seven databases: Medline, Web of Science, Cochrane, PubMed publisher, Google Scholar, Scopus, Embase. This search was conducted with the aid of a medical librarian (Dr. W. M. Bramer) of the Erasmus Medical Center, Rotterdam. We listed the search strings and databases in Appendix 1 to identify all articles concerning surgical treatment for recurrent CTS.

Study Selection

The PICOS categories (population, intervention, comparator, outcomes, and study design) were used to define study inclusion criteria. All published studies (prospective or retrospective) reporting outcomes of various surgical treatments for recurrent CTS, were considered for inclusion Subsequently, the abstracts and titles of published studies identified using the search terms were independently screened by two reviewers (M.C. and L.S.). Differences between reviewers were discussed until consensus was achieved. Next, from these articles, the full text was assessed based on the following eligibility criteria:

- Articles are written in English
- Original articles (no reviews)
- A minimum of 5 patients included in the study
- Articles concerning the surgical management of recurrent CTS
- Post-operative BCTQ or VAS pain were included in the reported outcome measurements
- Articles published after 1990

The quality of evidence of the included articles was based on The Oxford Centre for Evidence-based Medicine (OCEBM) Levels of Evidence system Specifications[28] (see Appendix 2). Subsequently, an assessment of bias has been conducted according to the quality assessment using the NIH tool for Series Studies[29] (Appendix 4 and 5). The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were followed[25]. The checklist is available in the online supplements of this article (Appendix 5).

Studies were assigned to one of the treatment groups; neurolysis, autologous fat transfer, hypothenar fat pad, pedicled flap and 'other' based on the reported intervention. The 'other' treatment group consisted of studies that were not suitable to be assigned to one of the previous treatment groups.

Data extraction

The following study details were extracted from the included studies: Study authors, publication year, number of hands treated, percentage of female patients, type of surgeries performed for recurrent CTS, mean time of follow up, and outcome measurements (BSTQ SSS/FSS and VAS pain).

Validated outcome measurements

The BCTQ covers two domains; The symptom severity scale (SSS) and the functional status scale (FSS), including eleven and eight items, respectively. Based on these items, a score between 1 and 5 (BCTQ; 1= no complaints, 5= maximum complaints possible) is calculated for the SSS and FSS separately. In a VAS pain score, patients rate their pain between 0 and 10 (VAS pain; 0=no pain, 10= worst pain imaginable).

Statistical analysis

As our primary analysis, we conducted a meta-analysis to compare the pooled improvement on the BCTQ and VAS pain between the different surgical techniques using the defined procedural categories. As our secondary analysis, we compared pooled reported postoperative treatment outcomes for the different surgical techniques for the management of recurrent CTS using the BCTQ and VAS pain. We used forest plots for both the primary- and secondary analyses.

Moreover, when standard deviations were not reported in the included studies, we estimated these based on the median, range, and sample size as described by *Hozo et al*[30]. Pooled means and effect sizes were calculated by using a random-effect model with the DerSimonian-Laird method. To test for differences between treatment groups, we used the method proposed by *Borenstein et al*.[31] Heterogeneity testing was performed by using the I^2 statistic.

Because of multiple testing, we considered a p-value smaller than 0.005 as statistically significant. All analyzes were performed using R studio version 3.6.3.

RESULTS

For the BCTQ five case-series and five pre-post studies without control groups were included. Considering the VAS pain, six pre-post studies without control groups were included. Figure 1 shows the inclusion process. Information on the included studies is depicted in Table 1.

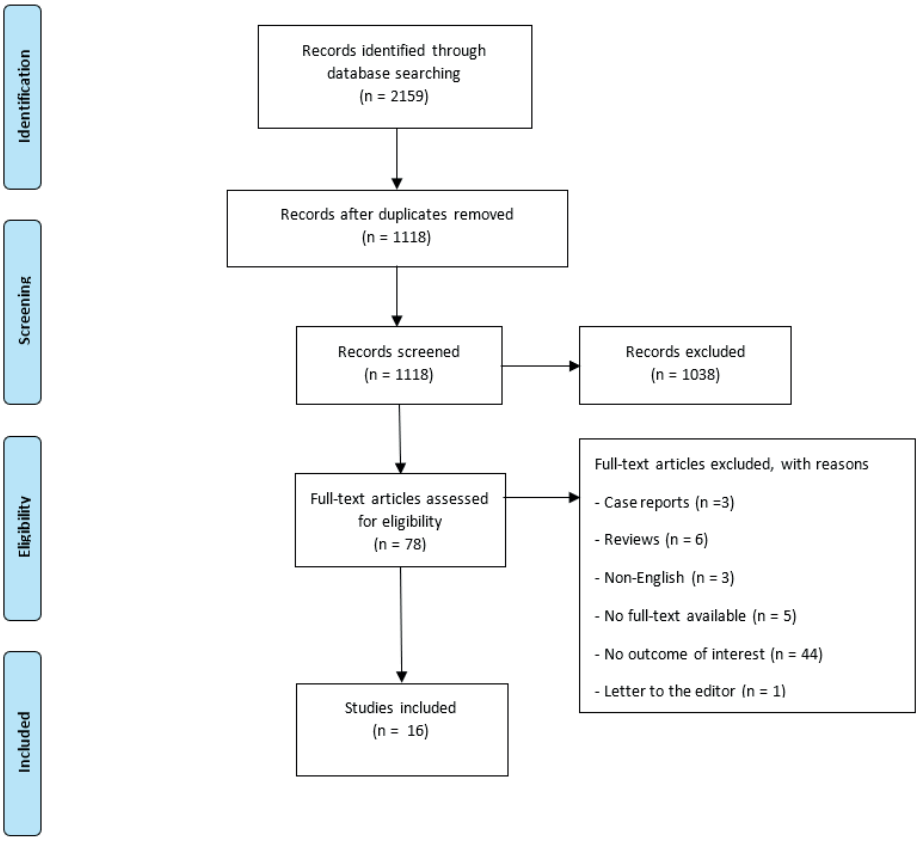

Figure 1. Flowchart of the selection of included articles.

Primary outcomes: The effect size of treatment effects

From the studies that reported pre-operative scores (Table 3), the pooled improvement can be compared between treatment groups. Five, four, and six studies were used to compare improvement on the SSS, FSS, and VAS pain respectively (Figure 2-4).

On the SSS, the amount of improvement [95%CI] for the neurolysis group was -1.1[-1.3;-0.9], for the autologous fat transfer group -1.2[-1.3;-1.1], for the hypothenar fat pad group -1.7[-2.2;-1.2], and for other techniques (e.g. neurolysis and the application of Mesofol) -0.8[-1.1;-0.6] on a 1-5 scale(Figure 2). When testing for subgroup differences, the amount of improvement was less for the 'other' group compared to the hypothenar fat pad (p=0.001) and the autologous fat transfer group (p=0.004).

On the FSS, the amount of improvement [95%CI] for the neurolysis group was -0.9 [-2.9;-1.0], for the hypothenar fat pad group -1.3[-4.0;-1.4], and other techniques group -1.1[-1.4;-0.93] (Figure 3) on a 1 to 5 scale. There were no statistical differences in improvement between the different techniques.

Table 1. Overview of BCTQ outcomes of revision surgery for recurrent CTS, per surgical technique

Author, year Level of Evidence	Number of hands treated (patients)	Number of women (%)	Surgical technique	Mean follow-up in months (range)	BCTQ – SSS (SD) post-operative	BCTQ – FSS (SD) post-operative
Neurolysis						
Cobb et al., 1996[13] Level IV	131 (131)	87 (66%)	Decompression with flexor tenosynovectomies (n=66) tenolyses (n=6), epineurotomies (=67) epineurectomies n=33), external neurolyses (n=92), internal neurolyses (n=19). Soft tissue flaps (n=11)	121 (24-276)	1.92 (0.82)	1.95 (0.90)
Impelmans et al., 2001[38] Level III	21 (20)	16 (80%)	re-decompression + external neurolysis	36 (2-100)	2.50 (0.20)	3.00 (0.20)
Luria et al., 2008[39] Level IV	41 (41)	13 (32%)	Endoscopic re-decompression	12	2.00 (0.30)	2.00 (0.20)
Pace et al., 2018[40] Level III	17 (17)	10 (59%)	Re-decompression	53 (16-155)	1.84 (0.81)	2.12 (1.36)
Sun et al., 2019[24] Level IV	114 (112)	84 (75%)	Re-decompression	6	1.91 (0.60)	1.92 (0.70)
Autologous fat transfer						
Impelmans et al., 2001[38] Level III	23 (20)	19 (91%)	Free fat graft	36 (2-100)	2.30 (0.20)	2.60 (0.20)
Hypothenar fat pad						
De Smet et al., 2002[41] Level III	8 (8)	6 (75%)	Hypothenar fat pad flap	31 (9-66)	2.70 (1.05)	2.55 (1.15)
Lattré, T. et al, 2016[42] Level III	8 (8)	6 (75%)	Hypothenar fat pad flap	12	1.09 (0.20)	1.16 (0.20)
Lattré, T. et al, 2016[42] Level III	8 (8)	5 (63%)	Hypothenar fat pad flap	12	1.22 (0.27)	1.14 (0.14)
Pace et al., 2018[40] Level III	16 (16)	7 (44%)	Hypothenar fat pad flap	53 (16-155)	2.54 (1.18)	2.50 (1.32)
Pedicled flap						
De Smet et al., 2002[41] Level III	6 (6)	3 (50%)	Distal ulnar fat flap	31 (9-66)	2.67 (0.71)	2.26 (0.71)
Goitz et al., 2005[43], Level IV	10 (7)	6 (86%)	Microvascular omental transfer	79 (54-105)	3.10 (0.70)	3.10 (0.90)
Other						
Nassar et al., 2014[22] Level IV	14 (14)	11 (79%)	Neurolysis and application of Mesofol	26 (18-39)	1.88 (0.37)	1.69 (0.35)
Sun. et al., 2019[23], Level IV	20 (18)	10 (56%)	Palmaris longus interposition	15 (7-26)	2.25 (range: 1.09 – 4.45)	2.18 (range 1.25 – 4.13)

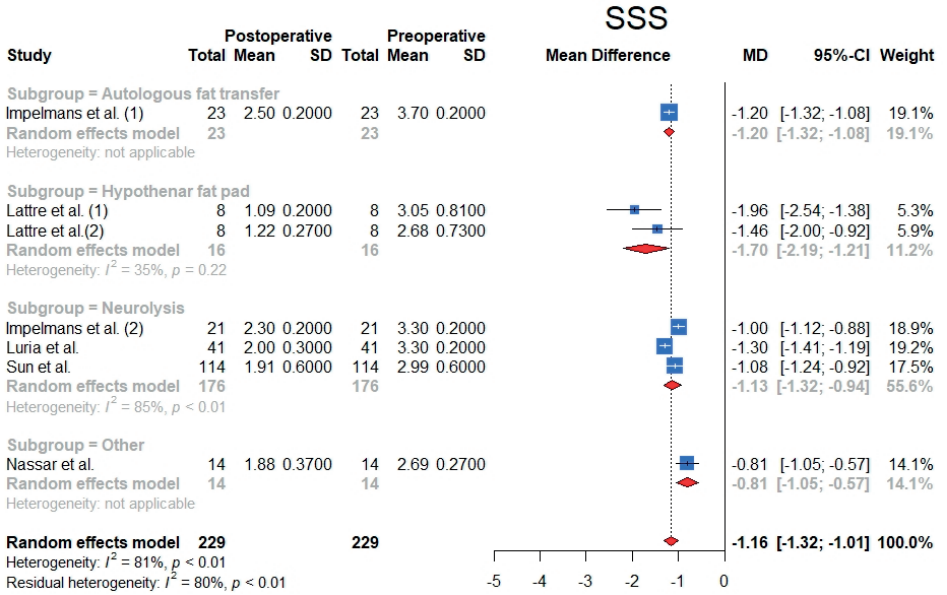

Figure 2. Forrest plot for the mean differences (MD) between pre- and post-operative BCTQ-SSS scores for the treatment groups autologous fat transfer, hypothenar fat pad, the neurolysis group and the 'other' group. Blue squares represent values reported in the study and the red diamonds represent the pooled MD for the treatment group. For the subgroup differences, the amount of improvement is significantly less for the 'other' group (e.g., neurolysis and the application of Mesofol) compared to the hypothenar fat pad (p=0.001) and the autologous fat transfer group (p=0.004).

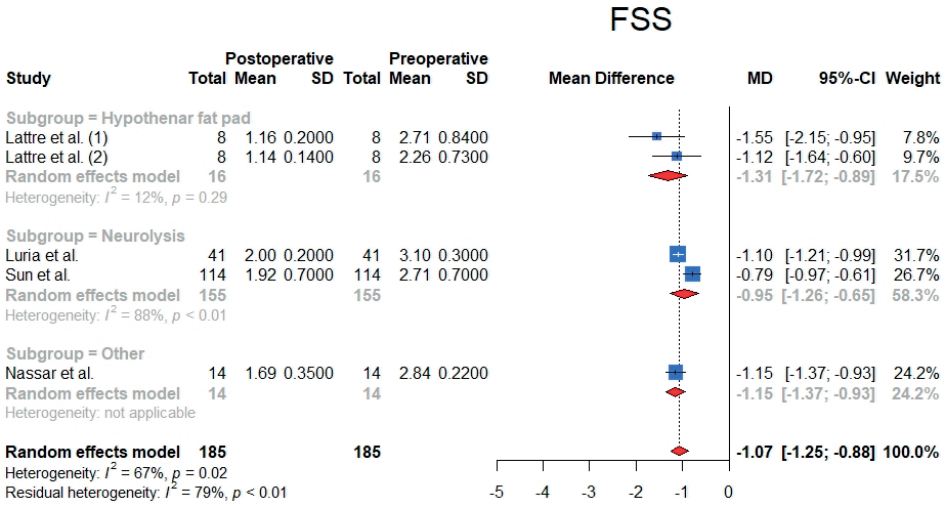

Figure 3. Forrest plot for the mean differences (MD) between pre- and post-operative BCTQ-FSS scores for the different treatment groups hypothenar fat pad, the neurolysis group and the 'other' group. In this figure, the blue squares represent the MD reported in the study and the red diamonds represent the pooled MD for the treatment group, with their width as the CI. When calculating subgroup differences, there were no statistical differences between subgroups.

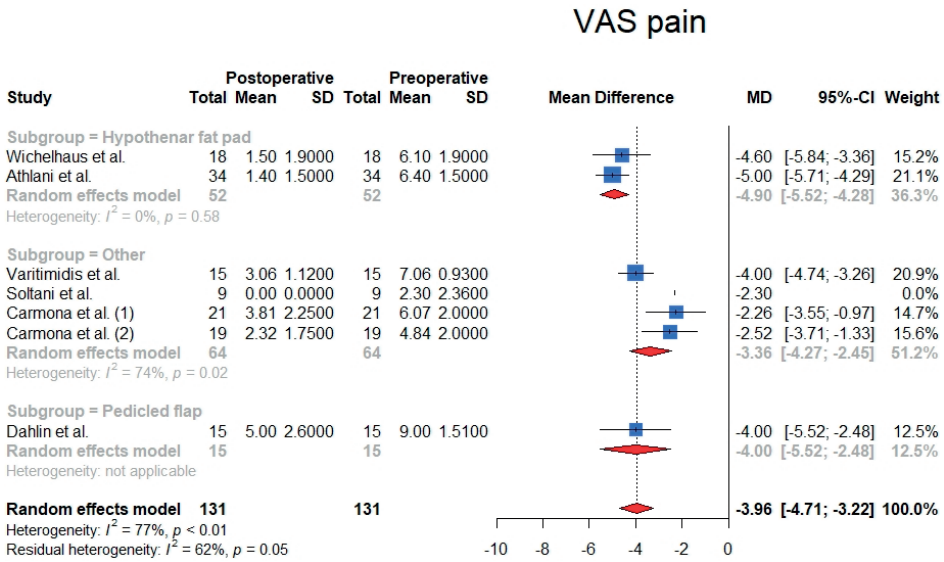

Figure 4. Forrest plot for the mean differences (MD) between pre- and post-operative VAS pain scores for the different treatment groups hypothenar fat pad, the pedicled flap and the 'other' group. In this figure, the blue squares represent the MD reported in the study and the red diamonds represent the pooled MD for the treatment group, with their width as the CI. When calculating subgroup differences[30], there were no statistical differences between subgroups.

On the VAS pain, the amount of improvement [95%CI] for the different treatment groups was -4.9[-7.1;-2.7] for the hypothenar fat pad group, -4.0[-5.5;-2.5] for the pedicled flap group, and -3.0[-5.4;-2.5] for the 'other' group (e.g. pedicled ulnar flaps, pedicled forearm flap, groin flap), on a 0 to 10 scale (Figure 4). There were no statistical differences in improvement between the different techniques.

For all outcomes, the forest plots in Figures 2-4 showed relatively high within subgroups heterogeneity (0-88%) between studies.

Secondary outcomes: Reported postoperative outcomes

The pooled average of the reported post-operative SSS outcomes, without taking pre-operative scores into account, was 2.1 [1.8;2.3]. The post-operative pooled means for the SSS of the different treatment groups can be seen in Figure 5. The reported postoperative SSS for the hypothenar fad pad group(1.8 [1.2;2.2]), the neurolysis group(2.0 [1.8-2.2]), and the 'other' group(2.0 [1.7-2.4]) were better compared to the pedicled flap group (2.9 [2.5-3.3])(p<0.005). Furthermore, the post-operative SSS for the hypothenar fat pad- and the neurolysis group were better compared to the autologous fat transfer(2.5 [2.4-2.6]) (p<0.005).

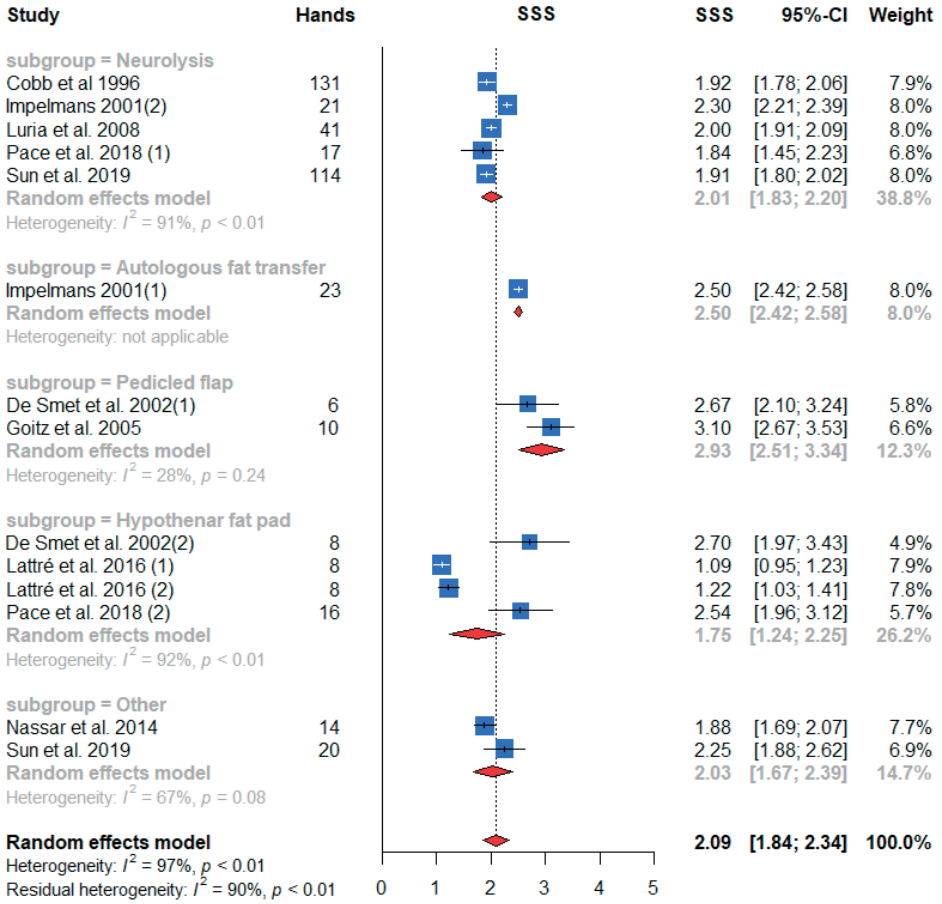

Figure 5. Post-operative pooled means for the post-operative BCTQ-SSS for the different treatment groups with CI for the different treatment groups hypothenar fat pad, the pedicled flap and the 'other' group. In this figure, the blue squares represent the MD reported in the study and the red diamonds represent the pooled MD for the treatment group, with their width as the CI. The postoperative SSS for the hypothenar fad pad group, the neurolysis group, and the 'other' group were significantly better compared to the pedicled flap group (p<0.005). Furthermore, the postoperative SSS for the hypothenar fat pad- and the neurolysis group were significantly better compared to the autologous fat transfer (p<0.005).

Considering the post-operative FSS-score, the ten included studies reported an average score of 2.1 [1.8-2.5]. The post-operative pooled means of the treatment groups can be seen in Figure 6. The hypothenar fat pad treatment- (1.6[1.2;1.9]), the neurolysis treatment-(1.9, [1.8;2.1]), and the 'other' treatment group (1.9, [1.4;2.4]) had better pooled reported postoperative outcomes compared to the autologous fat transfer (3.0 [2.9;3.1]) (p<0.005).

Considering the post-operative VAS pain score, studies reported an average score of 2.8 [2.0-3.6]. The post-operative pooled means for the VAS pain for the treatment groups can

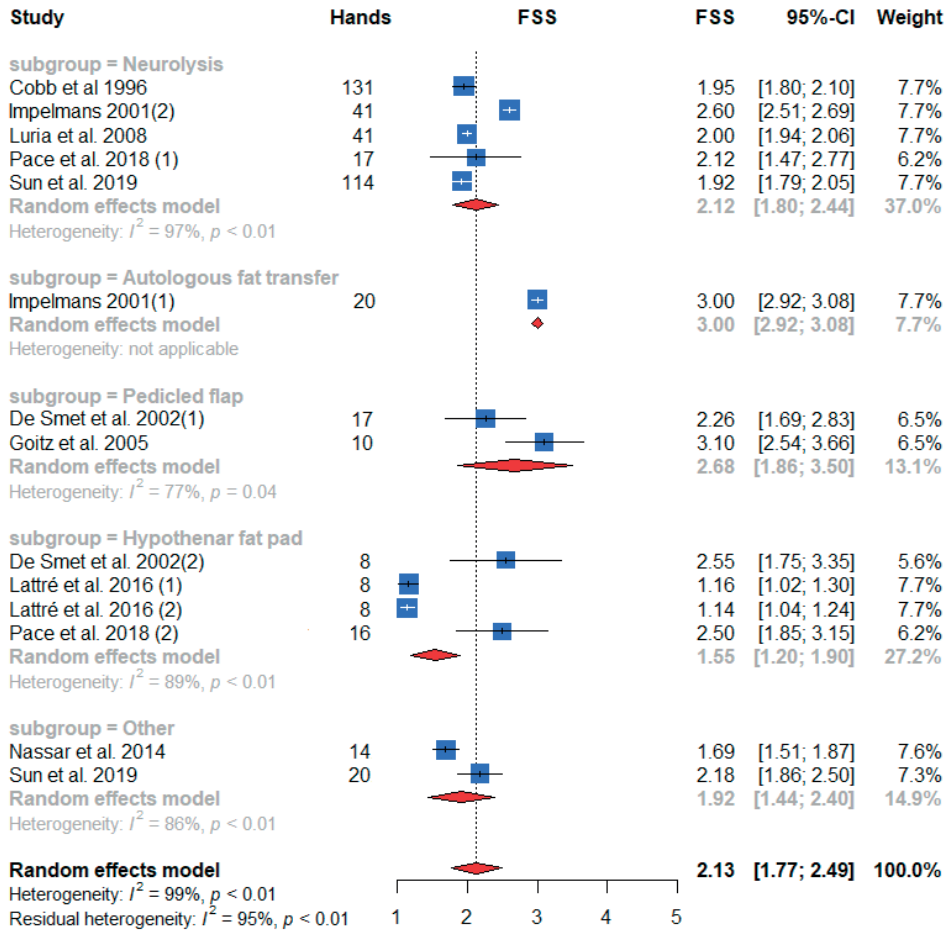

Figure 6. Post-operative pooled means for the post-operative BCTQ-FSS for the different treatment groups with a confidence interval. The hypothenar fat pad shows the best reported pooled post-operative FSS-score of the different surgical techniques for recurrent CTS, thus not taking in consideration pre-operative values. The hypothenar fat pad treatment group, the neurolysis treatment group, and the 'other' treatment group had significantly better pooled reported postoperative outcomes compared to the autologous fat transfer (p<0.005).

be seen in Figure 7. The pooled reported postoperative VAS pain score for the hypothenar fat pad treatment group (1.4 [0.83;2.1]) was better than for the 'other' group (3.0 [2.3;3.8]) (p<0.001).

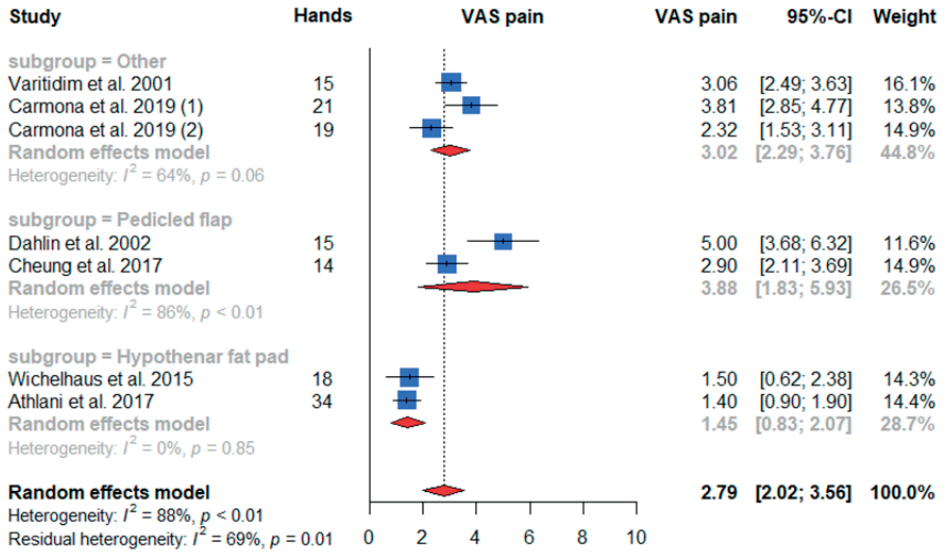

Figure 7. Post-operative pooled means for the post-operative VAS pain for the different treatment groups with a CI. The pooled reported postoperative VAS pain score of the hypothenar fat pad.

Table 2. Overview of VAS pain outcomes of revision surgery for recurrent CTS, per surgical technique

Author, year Level of Evidence	Number of hands treated (patients)	Number of women (%)	Surgical technique	Mean follow-up in months (range)	VAS pain 0-10 (SD) post-operative
Neurolysis					
Autologous fat transfer					
Hypothenar fat pad					
Wichelhaus et al., 2015[25], Level IV	18 (18)	14 (78%)	Hypothenar fat pad flap	22 (6-53)	1.5 (1.9)
Athlani et al., 2017[20], Level IV	34 (34)	15 (44%)	Hypothenar fat pad flap	36 (24-60)	1.4 (0-6)*
Pedicled flap					
Dahlin et al., 2002[44], Level IV	15 (15)	10 (67%)	pedicled ulnar flaps (n=5), pedicled forearm flap (n=1), groin flap (n=1), scapular flaps (n=3) free lateral arm flaps (n=5)	102 (3-168)	5.0 (1-10)*
Cheung et al., 2017[45], Level IV	14 (12)	7 (58%)	Abductor digiti minimi flap	44 (4-170)	2.9 (1.5)
Other					
Varitimidis et al. 2001[46], Level IV	15 (15)	9 (60%)	Autologous vein insulator	43 (24-78)	3.1 (1.1)
Carmona et al., 2019[21], Level III	21 (21)	16 (76%)	Canaletto device	12 (7-19)	3.8 (0-9)*
Carmona et al., 2019[21], Level III	19(19)	12 (63%)	Canaletto device and Dynavisc gel	11 (6-23)	2.3 (0-7)*

* = range

Table 3. Overview of studies reporting pre- and post-operative BCTQ scores for revision surgery for recurrent CTS, per surgical technique

Author, year	Number of hands (patients)	Surgical technique	Mean pre-operative BCTQ-SSS (SD)	Mean post-operative BCTQ-SSS (SD)	Δ BCTQ-SSS mean improvement (%)	Mean pre-operative BCTQ-FSS (SD)	Mean post-operative BCTQ-FSS (SD)	Δ BCTQ-FSS mean improvement (%)
Neurolysis								
Impelmans et al.., 2001 Level III	21 (20)	re-decompression + external neurolysis	3.3 (0.2)	2.3 (0.2)	1.0 (43%)			
Luria et al., 2008 Level IV	41 (41)	Endoscopic re-decompression	3.3 (0.2)	2.0 (0.3)	1.3 (57%)	3.1 (0.3)	2.0 (0.2)	1.1 (52%)
Sun et al., 2019 Level IV	114 (112)	Re-decompression	3.0 (0.6)	1.9 (0.6)	1.1 (55%)	2.7 (0.7)	1.9 (0.7)	0.8 (47%)
Autologous fat transfer								
Impelmans et al., 2001 Level III	23 (20)	Free fat graft	3.7 (0.2)	2.5 (0.2)	1.2 (44%)			
Hypothenar fat pad								
Lattré, T. et al, 2016 Level III	8 (8)	Hypothenar fat pad flap	3.1 (0.8)	1.1 (0.2)	2.0 (95%)	2.7 (0.8)	1.2	1.5 (88%)
Lattré, T. et al, 2016 Level III	8 (8)	Hypothenar fat pad flap	2.7 (0.7)	1.2 (0.3)	1.5 (88%)	2.3 (0.7)	1.1 (0.1)	1.2 (92%)
Pedicled flap								
Other								
Nassar et al., 2014 Level IV	14 (14)	Neurolysis and application of Mesofol	2.7 (0.3)	2.0 (0.3)	0.7 (41%)	2.8 (0.2)	1.7 (0.4)	1.1 (60%)

BCTQ = Boston Carpal Tunnel Questionnaire, SSS = Symptom Severity Scale, FSS = Functional Severity Scale

DISCUSSION

In this study, we reported validated outcomes measured using the BCTQ and the VAS pain score for different surgical procedures used in the management of recurrent carpal tunnel syndrome (CTS). The average improvement after surgery was -1.2 [-1.3;-1.0], -1.1[-1.3; -0.9], and -4.0[-4.7;-3.2] for the SSS, the FSS, and the VAS pain respectively. The pooled improvement for the different treatment options ranged from -0.8[-1.0;-0.6] to -1.7[-2.2;-1.2] for the SSS, -0.9[-2.9;-1.0] to -1.3[-1.7;-0.9] for the FSS, and -3.4[-4.3;-2.5] to -4.9[-5.5;-4.3] for VAS pain. When comparing improvements with the reported minimally clinical important difference (MCID), which is a difference of 0.8, 0.5, and 1.1 for the SSS, FSS and VAS pain respectively[32,33], the improvement for all the included surgical techniques was greater than the MCID. This means that, on average, all the included surgical treatments are on average effective for clinically relevant improvement.

When comparing improvement, we only found less improvement for the 'other' treatment group on the SSS compared to the hypothenar fat pad group and the autologous fat transfer group. We did not find differences between treatment groups when comparing improvement on the FSS and VAS pain. This might partially be explained by the limited number of studies and the heterogeneity between these studies available for analysis. However, when looking at the size of the improvement in outcomes (Figures 2-4), there may be a trend towards a greater improvement when recurrent CTS is treated using the hypothenar fat pad. Looking at the post-operative BCTQ and VAS pain scores (Figures 5-7), this trend may be supported by the favourable reported post-operative scores for the hypothenar fat pad compared to other techniques.

While the analyses of post-operative scores may be influenced by biases such as selection bias, the favourable reported post-operative outcomes for the hypothenar fat pad could be explained by the hypothesized advantages of this technique from literature. In literature, it has been stated that the hypothenar fat pad technique has the advantage that it is locally available, well-vascularized, and of sufficient size to provide cover to the median nerve[34,35]. Coverage of the median nerve with well-vascularized tissue is important for scar reduction, prevention of adhesions[10,35,36], and thereby restoration of nerve glide and improve outcomes[16,37]. Lastly, the hypothenar fat pad is a relatively simple procedure to perform[20] compared to other more extensive techniques. Therefore, using the hypothenar fat pad might lead to more predictable results for hand-surgeons with low treatment volumes for treating recurrent CTS.

To our knowledge, this is the first meta-analysis to compare outcomes of different surgical techniques for recurrent CTS using validated outcome measurements. While *Soltani et al.*[19] have conducted a systematic review to compare the efficacy of flap- and non-flap surgery for recurrent CTS, they compared the percentage of patients that experienced improvement/resolution on different treatment outcomes. They grouped the hypothenar

fat pad within the flap surgery treatment group for analysis. Furthermore, they found that flap surgery might lead to better success rates. While this is in line with our finding that the hypothenar fat pad flap has favourable reported outcomes, this effect may be explained by other types of flap surgery in the flap-surgery treatment group. However, the included studies by *Soltani et al.*[19] reported high success rates for the hypothenar fat pad (89-93%).

Several limitations of this study should be considered. First, when comparing outcomes, selection bias may play an important role. Patient characteristics between treatment groups might differ and, therefore, outcomes between treatments may not be comparable. However, from the information of the included studies, we were not able to correct for this in our analyses. Second, our forest plots showed variable within subgroup heterogeneity (0-88%) between studies. This means that these studies might have low comparability. However, this might partially be explained by the small sample sizes of the studies[38].

Third, for some analyses, only one study was available for a treatment group. Therefore, pooled values for these treatment groups might not be generalizable and should be interpreted with caution.

Fourth, the absence of standardization of the timing of outcome measurement further limits the conclusions that may be drawn. However, for the majority of patients, the outcomes were measured after more than a year post-operative. Therefore, outcomes are less likely to be influenced by patients recovering from surgery.

Fifth, the majority of the included studies were case-series or before-after studies with no control group. Therefore, the included studies did not have a high level of evidence. However, no studies of a higher level of evidence were available.

Sixth, we assumed patients underwent a complete division of the transverse carpal ligament during the primary procedure. Persistent CTS may have been inappropriately defined as recurrent CTS in some of the studies. Revision surgery and release of the residual compression points would resolve much of the symptoms without the need for the adjunctive procedures described.

A final consideration should be the evolution of surgical practice and the development and availability of biological materials and devices for implantation and modification of the healing process. There is no comparative data for these devices and future studies may need to include these interventions, creating further challenges for the acquisition of level one data.

In conclusion, our study showed some differences in improvement on the SSS, but not the FSS and the VAS pain between the treatment groups. However, there may be a trend towards a greater improvement when using the hypothenar fat pad. The reported postoperative scores on the BCTQ and the VAS pain favoured the hypothenar fat pad compared to the other treatment groups. The paucity of studies and the heterogenicity of the population in this review must be considered when interpreting the findings. Still, it is not clear which technique delivers the best outcomes, while there are big differences in invasive-

ness between techniques. While conducting a randomized controlled trial to determine the efficacy of different interventions in recurrent CTS will be challenging, further research with controlled prospective case-matched studies may be helpful in providing guidance to this clinical problem following a common surgical intervention in hand surgery.

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10 | General Discussion

1. MONITORING AND EVALUATING TREATMENT OUTCOMES OF CARPAL TUNNEL SYNDROME PATIENTS

The aim of **Part 1** of this thesis was to improve the collection of Patient Reported Outcome Measurements (PROM) in carpal tunnel syndrome(CTS) care by reducing the questionnaire length of one of the most commonly used PROM in the field: the Boston Carpal Tunnel Questionnaire(BCTQ). This way, response burden and response rates can be improved when measuring and monitoring outcomes for CTS care.

1.1 Item reduction of the BCTQ

The BCTQ is a widely used questionnaire in both clinical practice and research. Because of this, minimizing non-response by decreasing the response burden for patients is can have a big impact on the feasibility or routine clinical care evaluation. Therefore, by using a large dataset of CTS patients provided by Xpert Clinic, we analysed patterns in which the BCTQ was completed in **Chapter 2**. We analysed these patterns in around 10.000 completed BCTQ's by using the Chi-squared automatic interaction detection algorithm(CHAID)[1] and this way, create a decision tree version of the BCTQ (DT-BCTQ) based on the answer patterns of patients. By doing so, we were able to reduce the total amount of questions of the BCTQ needed to ask a patient from 18 to a minimum of 6 questions, 3 for the SSS, and 3 for the FSS. We did this while maintaining a high amount of agreement measured in an intercorrelation coefficient(ICC) of 0.94 with the original BCTQ. So far, no other study reduced the item length of both domains of the BCTQ. Atroshi et al.[2] did develop a six-item version of the symptom severity scale (SSS) domain of the BCTQ, also known as the CTS-6. The CTS-6 was created by using exploratory factor analysis and item response theory (IRT) analysis, which resulted in a six-item version of the SSS with an ICC of 0.80 with the original 11-item SSS.

Although the DT-BCTQ created in **Chapter 2** has a relatively high ICC with the original BCTQ, the DT-BCTQ is designed for electronic use only and is not practical to be used on paper. Therefore, the DT-BCTQ might be difficult to implement in practices with limited access to online technology. Moreover, other techniques to produce electronic versions of questionnaires to reduce item length are available such as computer adaptive testing (CAT)[3]. However, an advantage of a CHAID-based decision tree is that the decision tree is fixed and, therefore, technically easier to apply compared to CAT, which continuously needs to calculate the next-best question based on the previously administered questions. This requires specific CAT software and is often slow in presenting the next question to the patient. While a large database of completed BCTQ's is needed for the CAT algorithm to function properly, the DT-BCTQ can be implemented immediately.

In conclusion, by using the DT-BCTQ, the response burden for CTS patients can be reduced when monitoring and collecting outcomes on the widely used BCTQ while maintaining fair psychometric properties.

1.2 Recommendations for future research

Considering the DT-BCTQ created in **Chapter 2**, future studies are required to evaluate additional psychometric properties of the DT-BCTQ, such as the test re-test reliability and validity.

Moreover, future studies could test the influence of item reduction of the BCTQ on the response rate of patients. Furthermore, the use of CAT to reduce item length in the administration of the BCTQ has not been reported yet. While technologically more advanced, CAT might improve psychometric properties compared to the use of the CHAID-algorithm.

In clinical practice and research, the use of patient-reported outcome measurements is becoming increasingly more important[4]. Because of this, often, multiple questionnaires are presented to a patient, such as a quality of life questionnaire and patient-reported experience measures. Therefore, decreasing the length of each specific questionnaire is important to diminish the total response burden for the patient and, this way, increase response rates[5]. Because of technological advances, questionnaires are distributed more often electronically[6]. This provides new ways of distributing and administering questionnaires to patients and decrease response burden while maintaining fair psychometric properties, such as CAT or the use of the CHAID-algorithm. Because the use and collection of 'big data' are becoming more important in the medical field as well[7], the use of CAT-like techniques for the distribution of questionnaires to patients is likely to increase in the future. Future research should determine the influence of these item reduction techniques on the response burden and response rates of patients and could examine if these techniques are cost-effective in doing so. Furthermore, future research on using CAT-like techniques in clinical practice to reduce questionnaire length could examine if taking into account patient factors such as age, gender, comorbidities or occupation type into the algorithm would improve the precision of these techniques.

2. FACTORS INFLUENCING TREATMENT OUTCOME AFTER SURGICAL TREATMENT OF PRIMARY CARPAL TUNNEL SYNDROME

The aim of **Part 2** of this thesis was to determine which surgeon- and patient-related factors are of influence on the postoperative outcomes after a CTR for primary CTS. More specifically, we aimed to examine the influence of treatment volumes of surgeons and physical and psychological patient characteristics on CTS complaints and the return to work after CTR.

2.1 Predicting treatment outcomes for the surgical treatment of CTS for individual patients

In **Chapter 3,** we created a prediction model to predict the amount of symptom relief that a patient could expect on the BCTQ at six months post-operative when undergoing surgical treatment for primary CTS. In this chapter, we showed that the clinical severity of CTS at intake, as measured by the BCTQ, is the most important factor when estimating the amount of symptom relief after surgical treatment, as patients with more severe CTS experienced a greater effect of CTR on the BCTQ. Furthermore, we found that the presence of some specific comorbidities of the affected hand at baseline was predictive for a lesser amount of relief on CTS complaints. These comorbidities included the presence of trapeziometacarpal joint arthrosis, a trigger finger, instability of the wrist, and ulnar nerve neuropathy of the affected hand. In addition, we found that having a physically more demanding job is predictive for greater improvement of CTS symptoms. The results from **Chapter 3** can help to better understand the capabilities of a CTR in terms of symptom relief for different subgroups of patients. Moreover, these results provide information for the management of treatment expectations of patients undergoing surgical treatment for their CTS. It has been shown that pre-operative treatment expectations are of importance for the reported treatment outcomes of patients independent of the success of the CTR on a pathophysiological level[8].

By using multivariable models for the BCTQ and its domains, we could explain 37-41% of the variation in the treatment effect of CTR on the amount of symptom relief on the BCTQ. In **Chapter 3,** we showed that surgical treatment of primary CTS is, on average, effective in relieving CTS symptoms; however, because of the wide variation in the amount of symptom relief between individual patients, the mean improvement on symptoms might not be a relevant measure for individual patients.

While we found in **Chapter 3** that the presence of some specific comorbidities was associated with the amount of improvement on the BCTQ, this could also mean that the BCTQ might not be a reliable instrument when measuring treatment outcomes of CTS patients with comorbidities of the affected hand because patients might respond to the BCTQ based on the symptoms of these comorbidities as well. This could mean that the BCTQ is an insensitive outcome measure as it does not solely reflect median nerve dysfunction. This is of importance when the BCTQ is used to evaluate treatment outcomes in clinical practice. Therefore, patients with multiple comorbidities on the hand should be clearly counselled that they have symptoms related to more than one aetiology and that treatment for CTS is meant to address only the symptoms related to the median nerve compression. This information could be of importance in adjusting the individual patient expectations of the treatment for CTS.

In **Chapter 3,** 28 variables that might be suitable as predictors for the amount of symptom relief were tested. However, only a few variables were found to have predictive

value. In the literature, few and relatively small studies have performed similar analyses. However, still, a relatively large proportion of variance in treatment outcomes remains unexplained, suggesting other variables such as psychologic patient factors or surgeon-related factors might also play an important role.

2.2 The influence of surgeon treatment volume on postoperative outcomes after primary CTR

As described in **Chapter 3,** still a relatively large proportion of the explained variance in treatment outcomes after CTR is unknown. While patient-related factors are of importance in estimating the treatment effect of CTR, treatment outcomes might also be related to surgeon-related factors. For example, in the literature, the relation between the treatment volume of a surgeon on treatment outcomes have been described for multiple surgical techniques in the field of gastrointestinal-, cardiac-, lung-, and vascular surgery[9–12].Moreover, these studies have suggested beneficial effects from the centralization of some types of surgery. However, the influence of treatment volumes of a surgeon for the CTR procedure on treatment outcomes has not been examined so far. Therefore, in **Chapter 4** of this thesis, we analysed the relationship between treatment volume and treatment outcomes for open CTR by using multilevel random intercept linear regression analyses. By analysing the treatment outcomes of 1345 primary CTS patients operated by 17 different surgeons at the Xpert Clinic in The Netherlands, we found that there was no association between treatment volume and treatment outcomes at six months post-operative as measured on the BCTQ. We found that only 0.5-0.6% of the total variance in treatment outcomes on the BCTQ could be explained by the differences in treatment volume between surgeons. In addition, we did not find an association between treatment volume of surgeons and the number of complications of open CTR.

However, the most important limitation of this study was that all the surgeons included in this study were plastic surgeons specialized in hand surgery and operated at Xpert Clinic, which is a highly specialized hand clinic in the Netherlands. Although there was still a sufficiently wide range in treatment volumes (6 to 163 procedures per year) between surgeons to study the effect of treatment volumes on treatment outcomes, it could still be that the learning curve for open CTR flattens out at a relatively early stage that had already been passed by the surgeons in the study cohort.

Moreover, because all procedures were performed within one group of uniformly organized clinics with a similar patient population, we did not account for specific hospital volume-outcome relations. Previous research has shown an association between hospital volume and patient outcome, independent of the treatment volumes of surgeons[10,13]. More specifically, the relation between the number of patients undergoing a specific surgery at a specific hospital and their postsurgical outcomes indicate that hospitals with

higher treatment volumes deliver greater treatment outcomes, independent of individual surgeon treatment volumes.

Based on **Chapter 3** and **Chapter 4,** it can be concluded that still, a relatively large proportion of the variance of treatment outcomes is unexplained by the suggested patient- and surgeon related factors that were analysed in **Chapter 3** and **Chapter 4.** In literature, the influence of psychological patient factors on postoperative outcomes is becoming more clear for multiple surgical techniques[14–16]. Therefore, psychological patient factors might be of importance for post-operative treatment outcomes for CTR as well.

2.3 The influence of psychological patient factors on reported CTS complaints

Little is known on the importance of psychological patient factors on the subjective experience of CTS symptoms. Therefore, we analysed the influence of psychological patient factors such as illness perceptions, psychological distress, and pain catastrophizing on the reported CTS complaints in **Chapter 5**. We did this by analysing the relation between psychological patient factors and the reported CTS complaints on the BCTQ of 674 patients that were planned to undergo a primary CTR for CTS by using hierarchical linear models. **Chapter 5** showed that patients with CTS who are in more psychological distress, who have more catastrophic thoughts about pain, who interpret their illness as having more impact on their life and attributing more symptoms to the illness, experience their symptoms and hand function to be worse compared to patients who do not. These psychosocial factors explained an additional 20–25% of the variance in the difference in reported daily functioning and severity of the symptoms of CTS between patients. The results of **Chapter 5** are in line with previous studies that reported an association between pain catastrophizing and reported CTS complaints as well[17–20] . Moreover, our results are in line with previous studies that reported an association between anxiety and depression and worse reported CTS symptoms by patients[21,22].

The findings from **Chapter 5** might be of importance for clinical practice and the development of psychosocial interventions for patients with CTS. Furthermore, these findings support the importance of not only physical fitness but also the mental fitness of patients that undergo CTR to improve treatment satisfaction and outcomes[23]. The results of **Chapter 5** could give physicians more insight in the way CTS patients report their symptoms and function and that this also depends on how they perceive their illness, their mental health status, and the coping strategies that they use to deal with pain. Previous studies have shown the use of psychosocial intervention to improve the reported symptoms for other conditions than CTS[24,25]. Therefore, psychosocial interventions to improve the perceived symptom severity in patients with CTS might also be effective.

The most important limitation of **Chapter 5** is that it has a cross-sectional study design, which means that causality between the relation of psychological patient factors and the

reported health outcomes cannot be claimed. In other words, it is unclear to what extent worse psychological patient factors lead to worse reported health outcomes and to what extent worse health outcomes lead to worse psychological patient factors.

2.4 The influence of illness perception and mental health on return to work after carpal tunnel release

Because of the high estimated indirect costs of CTS, the return to work after the treatment of CTS is an important outcome measure[26]. While we discussed the relation between psychosocial patient factors and the subjective experience of symptoms and outcome of CTS patients in **Chapter 5,** the influence of psychological patient factors on the return to work after CTR is not well understood. Therefore, we examined the influence of illness perception and the mental health status of patients preoperatively on the return to work in the first six months after a CTR In **Chapter 6,** we showed that patients who worry more about their CTS complaints preoperatively are likely to return to work later in the first six months post-operative compared to patients who worry less about their CTS complaints, independent of the severity of their CTS. Moreover, we showed that patients who are having more faith preoperatively in a good effect of the planned CTR are more likely to return to work earlier in the first six months post-operative compared to patients who have less faith preoperatively in a good effect of the planned CTR. So far, only a few studies have examined the association between psychological patient factors and the return to work with variable results[27–30].

Differences in results might be attributed to the use of different measurement techniques to quantify psychological patient factors, the use of different statistical techniques to examine associations with the return to work or the use of different definitions for the return to work and psychological characteristics. One of the strengths of **Chapter 6** is that the analyses show effect sizes for specific psychological patient factors, corrected for other possible confounders. Also by using a Cox-model, the effect sizes are applicable for every time point within the first six months postoperative. This is in contrast with the majority of the previously performed research, where often uncorrected statistical tests are performed between subgroups of patients for the return to work on one specific time point after CTR.

However, a major limitation of **Chapter 6** would be that the return to work might be influenced by the recommendation of the surgeon or hand therapist[31]. At Xpert Clinic, recommendation on the return to work is mainly provided by the hand therapist. Hand therapists at Xpert clinic provide similar advice to all patients that certain actions such as pulling, pushing and putting weight on the operated are discouraged for ten to fourteen days. However, patients were able to decide when return to work was possible for their occupation based on their post-operative complaints and in consultation with the occupational physician when necessary. This might have influenced our results.

The findings in **Chapter 5** and **Chapter 6** support the importance of psychological patient factors on treatment outcomes for CTS and the subjective experience of symptoms by CTS patients. Moreover, addressing these psychological patient factors preoperatively might lead to low-cost intervention to improve treatment outcomes after a CTR.

2.5 Recommendations for future research

First, considering the prediction of the outcome of CTR for individual patients, it remains difficult to predict a precise outcome. In **Chapter 3** we found factors that explained 37-41% of the variance in the difference in treatment outcomes between patients. I suggest that future research takes into account psychological patient factors such as illness perception, pain catastrophizing, and mental health into account when trying to predict the outcome of CTR for individual patients.

Furthermore, the prediction models that were created in **Chapter 3** were not tested in an independent validation dataset. This is a major limitation of this study. Therefore, future research could focus on the validation of the created prediction models in independent datasets.

Moreover, because the improvement on the BCTQ does not always correspond well with the satisfaction after a CTR[32], future research could focus on the determinants of satisfaction after CTR as well. In addition, more advanced statistical methods might be needed to understanding the underlying associations between predictors and outcome after CTR, such as a random intercept model or machine learning.

Furthermore, based on the findings in **Chapter 3** that the BCTQ might not be a reliable measurement tool for CTS patients with comorbidities of the hand, future research should focus on the reliability of the BCTQ when measuring complaints of median nerve dysfunction in CTS patients who have comorbidities of the affected hand as well. This is of importance because often, patients with CTS also present themselves with other comorbidities of the hand, such as a trigger finger[33] or basal joint arthritis[34]. Likewise, in the population studied in **Chapter 3,** we found that in almost 40% of patients there was a presence of a trigger finger, trapeziometacarpal joint arthrosis, history of wrist trauma, De Quervain tenosynovitis, Dupuytren's disease, Guyon's canal syndrome, cubital tunnel syndrome or radial tunnel syndrome. This affects the use of the BCTQ in both research and clinical practice and is of importance when evaluating and interpreting treatment outcomes.

Another important topic of future research on the prediction of individual patient outcomes would be the integration of the prediction of outcomes in clinical practice. Until now, multiple predictors have been suggested to influence the outcome of the treatment of CTS[35–37]. However, the interpretation and integration of these predictors into clinical practice remains challenging. Because of technological advances and the desire for the use of big data in health care as well, integrating prediction models and decision tools into clinical practise is becoming more feasible. Still, little is known on the consequences of

integrating these decision tools and prediction models in clinical practice. Therefore, future research should focus on the practical implications of integrating prediction models in daily clinical practice and the treatment benefits that this integration might have. This could be an important topic of research because the integration of decision tools based on big data will likely increase in future clinical practice.

Second, considering the influence of treatment volumes on the outcomes, in **Chapter 4** we showed in a cohort of plastic surgeons highly specialized in hand surgery that treatment outcomes of open CTR are independent of treatment volumes of the surgeon. However, future research could focus on establishing this relationship for other physicians performing CTR such as orthopaedic surgeons, neurosurgeons, residents, or nurse practitioners to have a better understanding of the learning curve for the open CTR procedure. Because the open CTR is a common procedure performed all around the world, having more insight into the learning curve of open CTR could influence policies for CTS care. For example, previous research has shown that the outcomes of CTR performed by nurse practitioners are similar compared to the outcomes of CTR performed by plastic surgeons[38,39] while treatment costs differ. Therefore, examining ways in which open CTR could be performed by nurse practitioners could lead to more cost-effective CTS care.

Moreover, in **Chapter 4**, we did not take into account hospital-specific outcomes, while these could influence treatment outcomes independent of the treatment volumes of the surgeon[10,13]. Therefore, future research could focus on examining this relationship to gain more information on the benefits of centralization of CTS care, independent of increasing the treatment volumes of physicians.

Furthermore, in **Chapter 4** we examined the relationship between treatment volumes and treatment outcomes for open CTR. However, endoscopic CTR is thought to be technically more challenging than open CTR and might, therefore, have a different learning curve[40]. Future research could determine if a relationship between treatment volumes and treatment outcomes for endoscopic CTR exists. Likewise, little is known on the influence of treatment volumes of secondary carpal tunnel surgery on outcomes. Because treatment volumes are likely to be lower for secondary carpal tunnel surgery compared to primary carpal tunnel surgery, treatment volumes may be of importance for the treatment outcomes of secondary carpal tunnel surgery.

Moreover, considering **Chapter 5,** we showed in a cross-sectional study design that there is an association between illness perceptions, psychological distress, pain catastrophizing, and reported CTS complaints. However, because this is a cross-sectional design, we could not determine the direction of this association or imply causality. Because previous studies have shown that psychological intervention could improve reported complaints[41], future research should examine this relationship in more detail to determine if causality is present. More information on this relationship could lead to low-cost interventions to

improve CTS complaints and could lead to better identification of patients who are of risk for dissatisfaction after CTS treatment.

Last, considering **Chapter 6,** we showed that illness perception and mental health status influence the return to work in the first six months after a CTR, independent of the severity of CTS. Future research could determine if psychological intervention on high-risk patients for a prolonged return to work could improve the return to work as well. This could test the assumption supported by **Chapter 5, Chapter 6,** and *Wynter-Blyth V. et al*.[23] that not only physical fitness is of importance when patients are planned for surgical treatment, but also the mental state and illness perception.

3. FACTORS INFLUENCING TREATMENT OUTCOME AFTER SURGICAL TREATMENT OF SECONDARY CARPAL TUNNEL SYNDROME

While the aim of **Part 2** of this thesis was to determine which factors are of influence on the postoperative outcomes after a CTR for primary CTS, **Part 3** of this thesis aims to determine which factors are of influence on the postoperative outcomes of the surgical treatment of secondary CTS. More specifically, we looked at the differences in outcomes between primary CTS and secondary CTS patients in a propensity score matching study, examined predictive factors that predict the outcome of secondary CTS, and compared outcomes of different surgical techniques for the treatment of secondary CTS in a meta-analysis.

3.1 Comparing surgical outcomes between primary and secondary CTS patients

As described in the literature and in **Chapter 3**; surgical treatment is in general effective in relieving symptoms for primary CTS patients. However, revision surgery for secondary CTS is thought to be less effective. In **Chapter 7,** we showed that the outcome after revision CTR is worse compared to primary CTR, both uncorrected and corrected using propensity score matching on baseline characteristics. So far, this direct comparison between the outcomes of primary and secondary CTS has not been performed in previous studies. **Chapter 7** confirms the suggestion by previous studies that the effect of primary CTR might be larger than the effect of secondary CTR.

While we have shown that in general, the effect of CTR is smaller in patients with secondary CTS, still it is unknown which specific factors contribute to this. Secondary CTS has multiple etiologies such as an incomplete release, a misdiagnosis, or perineural fibrosis. While these factors could make revision surgery more difficult and are important to keep in mind, they have not yet been investigated as predictors of the outcome after revision surgery. Moreover, we were unable to include these factors in this study because these factors do not play a role in primary patients. In line with the results of **Chapter 5** where

we found an association between psychological patient factors and reported CTS complaints, previous research has shown that depression, pain catastrophizing and patients' expectations of treatment affects the reported outcomes after surgery[42]. A difference in psychological patient characteristics between primary CTS patients and secondary CTS patients might also influence the difference in the amount of effect between primary and secondary CTR.

Considering postoperative satisfaction, a higher percentage of primary patients (excellent/good: 76%) were satisfied with the outcome of CTR compared to secondary patients (55%). This difference seems higher compared to the differences in BCTQ outcome rates between the groups. This suggests that primary patients may be more likely to be satisfied with similar results than secondary patients.

Previous research has not only shown that psychological patient factors are of influence on the reported complaints of patients, but it has also been shown that psychological patient factors are of influence on the postoperative satisfaction[8,43,44]. In addition, postoperative satisfaction is best predicted by the fulfilment of expectations[8] which might be different between the primary CTS patients and the secondary CTS patients.

Several limitations of **Chapter 7** should be considered. Although we tried to reduce differences in baseline characteristics between the groups using propensity score matching, still residual confounding may be present. Second, a proportion of patients had missing values for BMI, smoking and alcohol use. We did not include these variables in the matching procedure since this would decrease the number of eligible patients and since previous studies showed that these variables are not related to the clinical outcome[35,37,45].

The results of **Chapter 7** can serve as a design for more accurate counselling of primary CTS patients and secondary CTS patients prior to surgery and provides new insights for future research.

3.2 Predicting the clinical outcome of revision surgery for recurrent and persistent carpal tunnel syndrome

Similar to the prediction of treatment outcomes of individual patients for the surgical treatment of primary CTS, it is difficult to predict treatment outcomes of secondary carpal tunnel surgery for individual patients. Therefore, the aim of **Chapter 8** was to create a prediction model to predict individual treatment outcomes for patients undergoing revision surgery for recurrent and persistent CTS. We did this by creating multivariable regression models for the SSS- the FSS-, and the total BCTQ-score at six months post-operative. To create this model, we used data that was collected in daily clinical practice from 112 patients that have undergone repeated decompression in the majority of the cases at one of the clinics of Xpert clinic in the Netherlands. By doing so, we found that a longer total duration of symptoms, a higher BCTQ total score at intake, and a diagnosis of complex regional pain syndrome along with CTS were associated with worse outcome after revi-

sion surgery at 6 months postoperatively. In addition, the multivariable prediction models could explain 33%, 23%, and 30% of the variance in the outcome as measured by the FSS, SSS, and BCTQ total scores, respectively, at 6 months post-operative. In present literature, only a few studies have assessed predictors of the outcome of revision surgery[35,46] and none of them used BCTQ scores as their primary outcome. The study of Zieske et al.[46] found that patients with more than 1 prior CTR and persistent symptoms have higher odds of worse postoperative pain. In addition, they found that pre-operative pain, pain medication consumption, and workers' compensation status to be significant predictors for the amount of post-operative pain.

Similar to the result in **Chapter 3** that the BCTQ score might be influenced by other comorbidities not related to median nerve dysfunction, the result that the presence of complex regional pain syndrome is predictive for the outcome of secondary carpal tunnel surgery might also be explained by the imperfect measurement properties of the BCTQ to solely measure median nerve dysfunction.

The results of **Chapter 8** can be used by surgeons and patients to manage patient expectations and identify subgroups of patients who benefit less or more from revision surgery and who are more likely to remain symptomatic.

3.3 The management of recurrent carpal tunnel syndrome

In the present literature, multiple techniques have been described for the treatment of recurrent CTS with variable results[47–53]. Although outcomes have been described for these different techniques in case series or pre-post studies without control groups, little comparative research has been conducted to compare treatment outcomes of different surgical techniques for recurrent CTS on validated outcomes measures. Therefore, we conducted a meta-analysis in **Chapter 9** to compare the reported treatment outcomes of different surgical techniques for the treatment of recurrent CTS on validated outcome measures such as the BCTQ and VAS pain. We did this by conducting a systematic literature search and assigned all eligible studies to one of the following treatment groups based on the intervention used in the study: neurolysis, autologous fat transfer, hypothenar fat pad, pedicled flap, and the 'other' treatment group. The 'other' treatment group consisted of studies that were not suitable to be assigned to one of the previous treatment groups. As ou primary outcome, we compared the pooled amount of improvement on the BCTQ and VAS pain between treatment groups. As our secondary outcome, pooled post-operative BCTQ and VAS pain values were compared between treatment groups. Based on the studies that were available, we found less improvement for the 'other' treatment group on the SSS compared to the hypothenar fat pad group and the autologous fat transfer group. Furthermore, we did not find differences between treatment groups when comparing improvement on the FSS and VAS pain. In addition, looking at the post-operative BCTQ and VAS pain scores, we found favourable reported postoperative scores for the hypothenar

fat pad compared to other techniques. To our knowledge, this is the first meta-analysis to compare outcomes of different surgical techniques for recurrent CTS using validated outcome measurements. However, multiple limitations should be considered. First, patient characteristics between treatment groups might differ and selection bias may have played an important role. Therefore, outcomes between treatments may not be comparable. However, from the information of the included studies, we were not able to correct for this in our analyses. Second, the forest plots in **Chapter 9** showed variable within subgroup heterogeneity (0-88%) between studies. This means that these studies might have low comparability. However, this might partially be explained by the small sample sizes of the studies[54] Third, for some analyses, only one study was available for one of the treatment groups. Therefore, pooled values for these treatment groups might not be generalizable and should be interpreted with caution.

3.4 Recommendations for future research

In **Chapter 7** we showed differences in outcome after primary and secondary surgery for CTS in propensity score matched patients. In addition, we found a relatively large difference between primary and secondary CTS patients in postoperative satisfaction. Future research could focus more on which factors influence these differences in postoperative outcomes and satisfaction. As stated earlier, it has been shown that psychological patient factors such as illness perception and pre-operative expectations play an important role in postoperative satisfaction[8]. Therefore, it would be interesting for future research to focus on the differences in psychological patient factors between primary and secondary CTS patients in terms of illness perception, pre-operative expectations and mental health. This could lead to a more tailored approach to the management of expectations for CTS patients.

Considering **Chapter 8**, future research is needed to improve the prediction of outcomes for individual patients that undergo surgery for secondary CTS. Furthermore, it may be beneficial to know in what way psychological patient factors play a role in satisfaction after secondary surgery for CTS and which factors are predictive for a good outcome after secondary surgery for CTS. Ultimately, a prediction model for individual patient predictions could spare patients treatments unlikely to succeed. Moreover, more specific subgroups of secondary CTS patients may be identified based on the type of symptoms that a patient has. This is in line with the need for a better understanding of outcomes for the different treatment options for secondary CTS surgery, as described in **Chapter 9**. This is important because there may be specific subgroups of patients that benefit more from a certain technique for secondary surgery for CTS. However, because recurrent and persistent CTS has a lower prevalence compared to primary CTS, collecting data to have enough power to do this kind of subgroup analyses will be challenging. Such as described in **Chapter 9**, research should focus on comparing the outcomes of different surgical techniques for the

treatment of secondary CTS. Although multiple studies have been published describing outcomes of specific surgical techniques for secondary surgery for CTS, little comparative studies have been conducted to compare the outcomes of different surgical techniques. While conducting a randomized controlled trial to determine the efficacy of different interventions in secondary CTS will be challenging, future research with, for example, controlled prospective case-matched studies may be helpful in providing guidance to this clinical problem in hand surgery.

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11 | General Summary

SUMMARY

Carpal tunnel syndrome (CTS) is the most common peripheral neuropathy in the general population, with an estimated prevalence of around 7% in the general population of people between 18 and 75 years of age[1,2]. Because of this relatively high prevalence, CTS leads to a decreased quality of life and high indirect and direct economic costs worldwide[3,4]. This thesis aims to improve the outcomes of CTS care by pursuing the following goals:

1) Improve the collection of patient-reported outcome measurements(PROM's) in CTS care by improving response-burden and, therefore, response-rate of PROM's. To realise this aim, we created a decision tree version of the Boston Carpal Tunnel Questionnaire[5](BCTQ).
2) Examine patient and treatment factors that might be of influence on the outcome of surgical treatment of primary CTS in terms of reported CTS complaints and return to work.
3) Examine patient and treatment factors that might be of influence on the outcome of the surgical treatment of secondary CTS in terms of reported CTS complaints.

Part 1: Collecting treatment outcomes from carpal tunnel syndrome patients

Part 1 of this thesis aimed to produce an electronic decision tree (DT) version of the Boston Carpal Tunnel Questionnaire (DT-BCTQ) using the Chi-squared automatic interaction detection (CHAID) algorithm to reduce questionnaire length of the Boston carpal tunnel questionnaire (BCTQ) while minimizing the loss of measurement properties. This way, response burden and, therefore, response rates may be improved. By creating the DT-BCTQ in **Chapter 2**, we diminished the number of questions needed to ask a patient from 18 to a maximum of six questions, three for each subscore, when administering the BCTQ. We did this while maintaining an ICC of 0.94 with the original BCTQ. Future research should focus on validating the DT-BCTQ in different CTS population and test if the DT-BCTQ leads to improved response-rates for the BCTQ.

Part 2: Factors influencing treatment outcome after surgical treatment of primary carpal tunnel syndrome

Part 2 of this thesis aimed to examine factors that influence the treatment outcomes for primary CTS. Moreover, the ability to predict which patients are likely to respond to CTR could spare patient-burden and the expense of treatment unlikely to succeed. Therefore, the aim of **Chapter 3** was to identify factors that can predict the outcome of surgical treatment of CTS and to determine the contribution of these factors in predicting the outcome at six months postoperatively for individual patients. In **Chapter 3** we found that the severity of CTS at baseline was associated with the amount of surgical improvement on the BCTQ,

while the presence of comorbidities was associated with a smaller effect of surgery on the BCTQ. The results of **Chapter 3** can be used as a tool to identify pre-operatively which CTS patients have a higher chance of substantial improvement from surgical treatment. We suggest that future research on predictive factors for a successful outcome after CTR may focus more on non-physical factors such as mental health, pre-operative expectations and illness perception.

While previous studies have shown that more experienced surgeons have better outcomes in a variety of different procedures, this relationship remains unknown for CTR. Therefore, the aim of **Chapter 4** was to assess whether there is an association between treatment volume and outcomes following open CTR. In **Chapter 4,** a total of 1345 patients were included, operated on by seventeen surgeons. In this population, less than 1% of the total variance in treatment outcome on the BCTQ could be explained by differences between surgeons, indicating no association between annual surgeon volume and outcome measures at 6 months postoperatively in these specialized hand surgeons.

In **Chapter 5,** we examined the influence of illness perceptions, pain catastrophizing and psychological distress on self-reported symptom severity and functional status in patients diagnosed with CTS. Here, we found correlations with the self-reported severity of symptoms and psychological distress, pain catastrophizing, consequences, identity, concern and emotional representation. Furthermore, these factors (except for concern) were also associated with self-reported severity, when adjusted for baseline characteristics and comorbidities. We showed that these psychosocial factors explained an additional 20–25% of the variance in self-reported severity of CTS. Clinicians should take the psychosocial factors into account when they consulted by patients with CTS.

Although multiple factors influencing the return to work after a CTR have been identified, little is known about the influence of psychological patient factors on the return to work. Therefore, **Chapter 6** aimed to identify which psychological factors play a role in the return to work after a CTR. In this chapter, we found that worrying about CTS and the presence of depressive symptoms was associated with a prolonged return to work in the first six months postoperative, independent of other factors such as the severity of CTS. When splitting our study population into two subgroups based on the median score for worrying about CTS, the difference in return to work between subgroups was one week on average. Likewise, when splitting our study population into two subgroups based on the median score for the presence of depressive symptoms, the difference in return to work between subgroups was also one week on average. Furthermore, we found that having faith preoperatively in a beneficial effect of the CTR was associated with an earlier return to work in the first six months postoperatively independent of other factors. When splitting our study population into two subgroups based on the median score of having faith preoperative in a beneficial effect of CTR, the difference in return to work between subgroups was one

week on average. Addressing the psychological factors found in **Chapter 6** preoperatively might lead to low-cost interventions to improve the return to work after CTR.

Part 3: Factors influencing treatment outcome after surgical treatment of secondary carpal tunnel syndrome

To our knowledge, no previous research has directly compared the outcome of primary and revision CTR in otherwise similar cohorts, nor investigated which factors may explain a possible difference in outcomes. Obtaining this knowledge could improve preoperative counselling of patients with recalcitrant CTS and create realistic expectations. Therefore, the aim of **Chapter 7** was to compare the mean outcome of primary with revision CTR, both uncorrected and corrected for baseline disease severity and demographic factors. **Chapter 7** shows that the outcome after revision CTR is worse compared to the outcome after primary CTR, but the differences are relatively small. Preoperative symptom severity, functional status and demographics may play a role, since correcting for this factors reduces the difference in outcomes between primary and revision CTR. These results can be used for counselling of patients prior to surgery.

The aim of **Chapter 8** was to evaluate the self-reported outcome of revision surgery in patients with recurrent and persistent CTS and to identify predictors of clinical outcome of revision surgery. In **Chapter 8,** we identified the total duration of symptoms, BCTQ total score at intake, and diagnosis of complex regional pain syndrome along with CTS as predictors of clinical outcome and confirmed that revision surgery significantly improves self-reported symptoms and function in patients with recurrent and persistent CTS. Patients with more severe CTS symptoms have greater improvement in symptoms at 6 months postoperatively than patients with less severe CTS, but 80% of patients still had residual symptoms at 6 months postoperatively. These results can be used to inform both patient and surgeon and can be used to manage expectations on the improvement of symptoms after the surgical treatment of secondary CTS.

Little comparison between outcomes of surgical techniques for recurrent CTS has been conducted. In **Chapter 9** we aimed to compare the outcomes of different surgical techniques on the BCTQ and the VAS for pain through a meta-analysis. Eligible studies were assigned to one of the treatment groups neurolysis, autologous fat transfer, hypothenar fat pad, pedicled flap, and the 'other' treatment group based on the intervention. The 'other' treatment group consisted of studies that were not suitable to be assigned to one of the previous treatment groups. As our primary outcome, we compared the pooled improvement on the BCTQ and VAS pain between treatment groups. As our secondary outcome, pooled post-operative BCTQ and VAS pain values were compared between treatment groups. In this chapter, we found less improvement in the 'other' treatment group compared to the hypothenar fat pad group and the autologous fat transfer group on the symptom severity scale domain of the BCTQ. We found that the hypothenar fat pad had

the best reported postoperative values in our secondary analysis. However, because of the limited number of the studies, small sample size, and study quality of the included studies, the results of **Chapter 9** should be interpreted with caution.

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12 | Nederlandse samenvatting

Carpaal tunnel syndroom (CTS) is de meest voorkomende perifere neuropathie in de algemene populatie, met een geschatte prevalentie van 7 procent in de populatie van personen tussen de 18 en 75 jaar oud[1,2]. Vanwege deze relatief hoge prevalentie leidt CTS tot een verminderde kwaliteit van leven en hoge directe en indirecte kosten wereldwijd[3,4]. Dit proefschrift heeft als doel om de uitkomsten van CTS zorg te verbeteren door te streven naar de volgende doelen:

1) Het verbeteren van het verzamelen van patiënt gerapporteerde uitkomstmaten (PROM's) in CTS zorg door de responslast te verminderen en daarmee het responspercentage te verbeteren. Om dit doel te realiseren hebben we een beslisboomversie van de Boston Carpal Tunnel Questionnaire (BCTQ) ontwikkeld.
2) Het onderzoeken van patiënt- en behandelingsfactoren die mogelijk van invloed kunnen zijn op de uitkomst van de chirurgische behandeling van primair CTS in termen van CTS klachten en het hervatten van werk na een operatie.
3) Het onderzoeken van patiënt- en behandelingsfactoren die mogelijk van invloed kunnen zijn op de uitkomst van de chirurgische behandeling van secundair CTS in termen van de postoperatief gerapporteerde CTS klachten door patiënten.

Deel 1: Het verzamelen van behandeluitkomsten van patiënten met CTS

Deel 1 van dit proefschrift is gericht op het produceren van een elektronische beslisboomversie van de BCTQ (DT-BCTQ) door gebruik te maken van het Chi-squared Automotic Interaction Detection (CHAID) algoritme om de lengte van de vragenlijst te verkorten, terwijl we het verlies op de meeteigenschappen minimaliseren. Op deze manier kan de responslast worden verminderd en daarmee het responspercentage worden verhoogd. Met het creëren van de DT-BCTQ in **Hoofdstuk 2** waren we in staat om het aantal vragen dat gesteld dient te worden aan een patiënt, wanneer de BCTQ wordt afgenomen, van achttien naar maximaal zes vragen te verminderen, maximaal drie voor elke subschaal. Dit hebben we gedaan met het behoud van een intercorrelatie coëfficiënt (ICC) van 0.94 met de originele BCTQ. In de toekomst zou onderzoek zich moeten richten op het valideren van de DT-BCTQ in verschillende populaties van CTS patiënten en het testen of de DT-BCTQ daadwerkelijk tot hogere responspercentages leidt.

Deel 2: Factoren die de uitkomst van chirurgische behandeling van primair CTS beïnvloeden

Deel 2 van dit proefschrift is gericht op het identificeren van factoren die de behandeluitkomst van de chirurgische behandeling van primair CTS beïnvloeden. Het vermogen om preoperatief te voorspellen welke patiënten een grote kans hebben op een succesvolle ingreep voor CTS kan mogelijk onnodige belasting van de patiënt en onkosten van een ingreep met weinig kans van slagen, voorkomen. Daarom is het doel van **Hoofdstuk 3** om preoperatieve factoren te identificeren die de behandeluitkomst van de chirurgische

behandeling van CTS kunnen voorspellen en het bepalen van de predictieve waarde van deze factoren in het voorspellen van individuele behandeluitkomsten op zes maanden na operatie. In **Hoofdstuk 3** vonden we dat de ernst van CTS op baseline het sterkste geassocieerd is met de mate van chirurgische verbetering op de BCTQ, terwijl de aanwezigheid van comorbiditeiten van de hand geassocieerd is met een kleinere chirurgische verbetering van uitkomsten. De resultaten van **Hoofdstuk 3** kunnen worden gebruikt om preoperatief CTS patiënten te identificeren die een hogere kans hebben op een substantiele verbetering door chirurgische behandeling. Wij stellen voor dat toekomstig onderzoek naar predicitieve factoren voor een succesvolle uitkomst van de chirurgische behandeling van CTS zich richt op het onderzoeken van niet-fysieke factoren zoals mentale gezondheid, pre-operatieve verwachtingen en ziekte perceptie.

Terwijl eerder verricht onderzoek voor verschillende behandeltechnieken heeft aangetoond dat meer ervaren chirurgen betere behandeluitkomsten laten zien, is het nog onbekend of deze relatie ook bestaat voor het uitvoeren van een carpaal tunnel release (CTR). Daarom was het doel van **Hoofdstuk 4** om vast te stellen of er een relatie bestaat tussen de behandelaantallen van een chirurg en de behandeluitkomsten bij een open CTR. In **Hoofdstuk 4** werden 1345 patiënten geïncludeerd en geopereerd door zeventien verschillende chirurgen. In deze populatie, minder dan één procent van de totale variantie in behandeluitkomsten op de BCTQ kon verklaard worden door verschillen in behandelaantallen tussen verschillende chirurgen. Dit wijst op de afwezigheid van een associatie tussen de behandelaantallen van de chirurg en de behandeluitkomsten op zes maanden postoperatief bij de gespecialiseerde handchirurgen geïncludeerd in dit hoofdstuk.

In **Hoofdstuk 5** onderzochten we de invloed van ziekte perceptie, pijn catastrofen en psychologische stress op de zelf gerapporteerde ernst van symptomen en de functionele status van patiënten gediagnosticeerd met CTS. In dit hoofdstuk hebben we correlaties gevonden tussen de zelf gerapporteerde ernst van symptomen en psychologische stress, pijn catastroferen, perceptie van ziekte consequenties, perceptie van ziekte identiteit, zorgen maken over de aandoening en de emotionele representatie van de patiënt. Bovendien waren al deze factoren, op zich zorgen maken over de aandoening na, geassocieerd met zelf gerapporteerde ernst van symptomen wanneer er gecorrigeerd wordt voor baseline karakteristieken en comorbiditeiten. We hebben aangetoond dat deze psychosociale factoren een extra 20 tot 25 procent van de variantie in zelf gerapporteerde ernst van symptomen verklaart. Clinici zouden rekening met deze psychosociale factoren kunnen houden in de consultvoering met CTS patiënten.

Hoewel meerdere factoren in kaart zijn gebracht die de tijd tot het hervatten van het werk beïnvloeden na een CTR, is er nog weinig bekend over de invloed van psychologische factoren op tijd tot het hervatten van het werk. Daarom is **Hoofdstuk 6** gericht op het identificeren van de psychologische factoren die een rol spelen in de tijd tot het hervatten van het werk na een CTR. In dit hoofdstuk hebben we gevonden dat het zorgen maken over

CTS en de aanwezigheid van depressieve symptomen preoperatief geassocieerd zijn met een verlengde tijd tot het hervatten van het werk in de eerste zes maanden postoperatief, onafhankelijk van andere factoren, zoals de gerapporteerde ernst van de symptomen. Wanneer we de studie populatie in twee subgroepen splitsen op basis van de mediaan score voor het item zorgen maken over CTS, was het verschil in de tijd tot het hervatten van het werk na een CTR gemiddeld één week tussen de subgroepen. Insgelijks, wanneer we de studiepopulatie in twee subgroepen splitsen op basis van de mediaan score voor de aanwezigheid van depressieve symptomen, is het verschil in de tijd tot het hervatten van het werk gemiddeld één week tussen de subgroepen. Bovendien hebben we gevonden dat preoperatief vertrouwen hebben in een goed resultaat van de behandeling, de tijd tot het hervatten van het werk na een CTR verkort, onafhankelijk van andere factoren. Wanneer we de studie populatie splitsen in twee subgroepen op basis van de preoperatieve mediaan score op het item vertrouwen hebben in een goed resultaat van de behandeling, is het verschil in tijd tot het hervatten van het werk na een CTR gemiddeld één week tussen de subgroepen. Het preoperatief adresseren van de psychologische factoren uit **Hoofdstuk 6** kan mogelijk lijden tot goedkope interventies om de tijd tot het hervatten van het werk na een CTR te kunnen verbeteren.

Deel 3: Factoren die de uitkomst van chirurgische behandeling van secondair CTS beïnvloeden

Zover wij weten heeft geen eerder onderzoek direct de uitkomsten van primair en recidief CTR met elkaar vergeleken in vergelijkbare cohorten of onderzocht welke factoren een mogelijk verschil in uitkomsten kan verklaren. Het verkrijgen van deze kennis kan het preoperatief counselen van patiënten met secundair CTS verbeteren en helpen om realistische verwachtingen te creëren bij patiënten. Daarom was het doel van **Hoofdstuk 7** om de gemiddelde uitkomst van een primaire CTR te vergelijken met die van een secundaire CTR, zowel ongecorrigeerd als gecorrigeerd voor ernst van de ziekte en demografische factoren. **Hoofdstuk 7** laat zien dat de uitkomst van een secundaire CTR gemiddeld slechter is vergeleken met de uitkomst van een primair CTR. Echter, de verschillen in uitkomst zijn relatief klein. Preoperatieve ernst van symptomen, functionele status en demografische factoren spelen mogelijk een rol in het verklaren van de verschillen in uitkomsten gezien het toepassen van een correctie voor deze factoren de verschillen tussen de groepen verkleint. De resultaten uit dit hoofdstuk kunnen gebruikt worden voor het counselen van patiënten voorafgaand aan de operatie.

Het doel van **Hoofdstuk 8** was om de zelf gerapporteerde uitkomst van revisie chirurgie voor patiënten met recidiverend en persisterend CTS in kaart te brengen. In **Hoofdstuk 8** hebben we de duur van de symptomen, de BCTQ totale score op intake en een diagnose van complex regionaal pijn syndroom naast CTS geïdentificeerd als predictoren voor de klinische uitkomst. Daarnaast hebben we bevestigd dat revisie chirurgie significant de zelf

gerapporteerde ernst van symptomen en functie verbeteren voor patiënten met secundair CTS. Patiënten met ernstigere CTS symptomen hebben een sterkere verbetering van symptomen na zes maanden postoperatief ten opzichte van patiënten met minder ernstige CTS symptomen. Echter, 80 procent van de patiënten had nog steeds resterende symptomen na zes maanden postoperatief. Deze resultaten kunnen gebruikt worden om zowel de patiënt als de chirurg beter te informeren over de mogelijkheden van de chirurgische behandeling van secundair CTS en om de verwachtingen over de mate van verbetering van symptomen na een chirurgische behandeling voor secundair CTS beter te managen.

In de literatuur zijn er weinig vergelijkende studies uitgevoerd waarbij de uitkomsten van verschillende operatietechnieken voor recidiverend CTS met elkaar worden vergeleken. Het doel van **Hoofdstuk 9** was om de uitkomsten van verschillende operatietechnieken op de BCTQ en VAS pijn met elkaar te vergelijken door het uitvoeren van een meta-analyse. Geschikte studies werden ingedeeld in één van de behandelgroepen: neurolyse, het gebruik van autoloog vet, hypothenar fat pad, pedicled flap, en de 'overige' behandelgroep op basis van de interventie gebruikt in de studie. De 'overige' behandelgroep bestond uit studies waarbij de interventie niet overeenkwam met één van de eerder genoemde behandelgroepen. Als onze primaire uitkomstmaat hebben we de gepoolde verbetering op de BCTQ en VAS pijn vergeleken tussen behandelgroepen. Als onze secondaire uitkomstmaat hebben we de gepoolde postoperatieve waarden op de BCTQ en VAS pijn tussen behandelgroepen vergeleken. In dit hoofdstuk hebben we gevonden dat er een kleinere verbetering is in de 'overige' behandelgroep vergeleken met de hypothenar fat pad groep en de behandelgroep waarbij autoloog vet werd gebruikt op de symptoom intensiteit schaal van de BCTQ. Daarnaast vonden we dat de hypothenar fat pad over het algemeen de beste gerapporteerde postoperatieve waarden had in onze secundaire analyse. Echter, vanwege het kleine aantal studies, de kleine populatie groottes en de lage kwaliteit van de geïncludeerde studies is het van belang dat de resultaten van **Hoofdstuk 9** bedachtzaam geïnterpreteerd worden.

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List of publications in this thesis
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Predicting Clinical Outcome After Surgical Treatment in Patients With Carpal Tunnel Syndrome
M.C. Jansen, S. Evers, H.P. Slijper, K.P. de Haas, X. Smit, S.E. Hovius, R.W. Selles
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mij als paranimf terzijde staan. Wij bewandelen het leven samen, dezelfde basisschool, dezelfde middelbare school en zelfs dezelfde studie aan dezelfde universiteit. Voor buitenstaanders is dit soms wat gek, maar ik zou het niet anders hebben gewild. Wij hebben elkaar kunnen helpen in moeilijke tijden. Samen sparren voor moeilijke examens en tentamens. Ik heb de mijlpalen in mijn carrière voor een groot deel aan jou te danken. Als kind hadden wij onze eigen taal die wij met elkaar spraken met eigen verzonnen woorden die niemand begreep (zelfs wijzelf niet). Hoewel deze taal nu wel bestaat uit echte woorden, praten we nog steeds onze eigen taal en hebben we vaak aan een half woord genoeg. Jouw bescheidenheid in de talenten die je bezit, sieren jou. Sinds kort is ons gezamenlijke pad tot een kruispunt gekomen, waarbij jij de kant van de psychiatrie bent opgegaan. Jouw patiënten zullen in goede handen zijn bij zo'n getalenteerde psychiater in spe!

Dank aan Philip, voor al je hulp en steun tijdens mijn promotietraject. Met een doctor die cum laude gepromoveerd is als paranimf aan mijn zijde, moet de verdediging van dit proefschrift helemaal goed komen. Met hopelijk straks twee gepromoveerde doctoren in ons gezin hoef ik jou als klinisch geneticus in spe niet uit te leggen dat dingen onderzoeken in ons DNA zit. De overgave waarmee jij je in iets kan storten is bewonderingswaardig. Of het nou sporten, onderzoek of het leren van een nieuw muziekinstrument is, als jij je ergens aan over geeft, wordt het een succes. Door deze winnaars-mentaliteit is er niets wat jou tegenhoudt om jouw doelen en dromen in het leven waar te maken.

Dank aan Victor, voor al je steun. Als oudste van de kinderen geef je ons raad over de paden die jij als eerste al hebt bewandeld. Ik dank je voor al je oprechte telefoontjes om te vragen hoe het gaat. Als oogarts heb jij een scherpe blik op wat jij belangrijk vindt in het leven. Naast al het harde werk zorg je dat je niet vergeet te genieten van het leven met vrouw en kind(eren) en met je vrienden. Je bent een echt gezelschapsmens en hebt veel charisma. Ik heb bewondering voor jouw talent om mensen te verbinden. Uiteindelijk zijn het de momenten met familie en vrienden die het leven mooi maken!

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Dank aan Sophie, dat je in mijn leven bent. Zonder jou was dit alles niet gelukt. Na een lange dag werken, ben jij mijn veilige thuisbasis. Thuis is voor mij geen plek, maar een persoon. Ik dank je voor al je steun en begrip op de momenten dat ik het druk had. Ook wil ik je bedanken voor de prachtige voorkant die je hebt gemaakt voor dit proefschrift. Mijn successen zijn jouw successen. Dat wij samen nog vele mijlpalen mogen vieren! Zolang wij elkaar hebben, hebben wij niet veel nodig om gelukkig te zijn. Voor mij is dat echte liefde.

CURRICULUM VITAE

Miguel Jansen was born on the 28th of December 1993 in Utrecht, The Netherlands. After graduating with honors from *College de Heemlanden*, he started medical school in 2012 at the Erasmus Medical Center (Erasmus MC) in Rotterdam. Early in medical school, Miguel became interested in scientific research. Because of this, he started a research master in Health Sciences from The Netherlands Institute of Health Sciences (NIHES) in Rotterdam in 2015 to gain profound knowledge on conducting epemiological reseach. During medical school, Miguel became intrigued by the workings of the hand and the field of hand surgery. Therefore, Miguel choose the subject of carpal tunnel syndrome as his research subject for his master in Health Sciences and started his research career at the department Plastic, Reconstructive, and Hand Surgery of the Erasmus MC as part of the researchgroup; the HandWristStudyGroup. During this master, Miguel started his first researchproject on developing predictionmodels to preoperatively predict clinical outcome after carpal tunnel surgery. This researchproject was conducted with the help of S. Evers, H.P. Slijper, K. P. de Haas, X. Smit, S.E.R. Hovius, and under the supervision of Dr. R.W. Selles. Subsequently, Miguel started multiple other researchprojects in the field of carpal tunnel syndrome. After completing medical school and obtaining his medical degree in early 2020, Miguel continued working on these researchprojects as a PhD-student which eventually led to the completion of this thesis.

During his master from the NIHES, Miguel gained interest in the workings of the Dutch healthcare system. Therefore, he obtained a master in Health Economics, Policy & Law at the Erasmus University in Rotterdam in 2017. As a result, Miguel developed himself as an broad expert of healthcare as a whole. By obtaining a medical degree, a degree in epidemiology, and a degree in health economics, the ambition of Miguel is building bridges between these important pillars of healthcare.

Since December 2020, Miguel has been working at the department of Surgery of the Albert Schweitzer Hospital in Dordrecht.

In addition to his medical and researchcareer, Miguel started *MedSocks* in 2019, a company which fabricates and sells colorful socks in different medical themes, together with his companion D. van der Does. A part of the revenue is donated to different medical and social orientated charities, matching the themes of the socks. By doing so, MedSocks has already donated over more than €10.000 to charity, donated socks to the homeless, and donated stuffed animals to children in hospitals.

For the future, Miguel aspires to be the link between clinic, research and healthcare management.

PHD PORTFOLIO

Name PhD student: M.C. Jansen **Erasmus MC Departments:** - Plastic, Reconstructive and Hand Surgery - Rehabilitation Medicine	PhD period **Promotor(s)** I.M.J. Mathijssen **Supervisor** J.M. Zuidam R.W. Selles

1. PhD training

	Year	Workload (Hours/ECTS)
General courses		
Researchmaster Health Sciences *Netherlands Institute for Health Sciences*	2015-2020	120 ECTS
Master Health Economics, Policy & Law *Erasmus School of Health Policy & Management*	2016-2017	60 ECTS
Specific courses (e.g. Research school, Medical Training)		
Summercourses at The Harvard T. H. Chan School of Public Health: *Course: Fundamentals of Epidemiology* *Course: Society and Health*	2016	4.2 ECTS
Seminars and workshops		
Presentations		
Presentation on 'Predicting clinical outcome after surgical treatment in patients with carpal tunnel syndrome' at the Federation of European Societies for Surgery of the Hand (FESSH)	2018	10 hours
Presentation on 'Item reduction of the Boston Carpal Tunnel Questionnaire using decision tree onderwijsmodelling' at the Federation of European Societies for Surgery of the Hand (FESSH)	2018	10 hours
National and international conferences		
FESSH 2018 Congress Working for the Future	2018	30 hours
Other		
Application Value Based Health Care prize - Xpert Clinic, Erasmus MC, Handtherapie Nederland	2017	30 hours
Reviewing articles for peer-reviewed journals in the field	2020	15 hours

2. Teaching

	Year	Workload (Hours/ECTS)
Correcting exams for the academic training of first year medical students	2020	3 hours
Contributing to a course on how to handle and analyse HandWristStudyGroup data in R.	2020	50 hours
Lecture on how to conduct meta-analyses for medical students.	2020	10 hours

Miguel C. Jansen
Erasmus University
Rotterdam 2021