

## Osteoarthritis of the first carpometacarpal joint – Patients' subjective symptoms related to surgical outcome

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### ABSTRACT

**Objectives:** Osteoarthritis (OA) of the first carpometacarpal joint (CMC 1) is common and prevalence increases with age. Pain and disability impair daily life activities. The aim was 1) to evaluate outcome, with special interest in patient-rated functional outcome measures with the Quick Disability of Arm, Shoulder and Hand questionnaire (QuickDASH) after primary surgical treatment with ligament reconstruction and tendon interposition (LRTI) due to OA and 2) to clarify remaining postoperative symptoms, adverse effects and costs for treatment.

**Methods:** In the retrospective study, 54 patients (55 primary surgeries; response rate 33/54 patients, 61%; 33/55 surgeries, 60%) were reviewed with QuickDASH preoperatively and after one year. Data were also obtained from the patients' declaration of health and patient folders.

**Results:** Surgery resulted in reduced QuickDASH score [from 52 (42-72) to 34 (13-51),  $p=0.0001$ ]. Twenty-eight (85%) surgeries out of 33 were dismissed from outpatient care at a final follow-up visit within one year [median rehabilitation period 111 (67-179) days]. Nineteen (68%) out of these 28 patients still suffered from symptoms or adverse effects at the last visit, mostly related to pain. No differences were found between smokers and non-smokers. The five patients, not concluded within one year, required further conservative treatment and/or surgical procedures due to various symptoms. Total median costs for treatment were US\$ 3436 (3147-3949) [€ 2593 (2374-2979)].

**Conclusions:** Patients with OA of the CMC 1 joint benefit from surgery, but the procedure is associated with lengthy rehabilitation and persisting postoperative symptoms; meticulous preoperative information should be provided to patients.

**Key words:** CMC1 joint, interposition arthroplasty, LRTI, osteoarthritis, QuickDASH, thumb base, trapezium excision

### Introduction

Osteoarthritis (OA) in the first carpometacarpal joint (CMC 1) is associated with both pain and disability [1], most frequently appears in women, increases

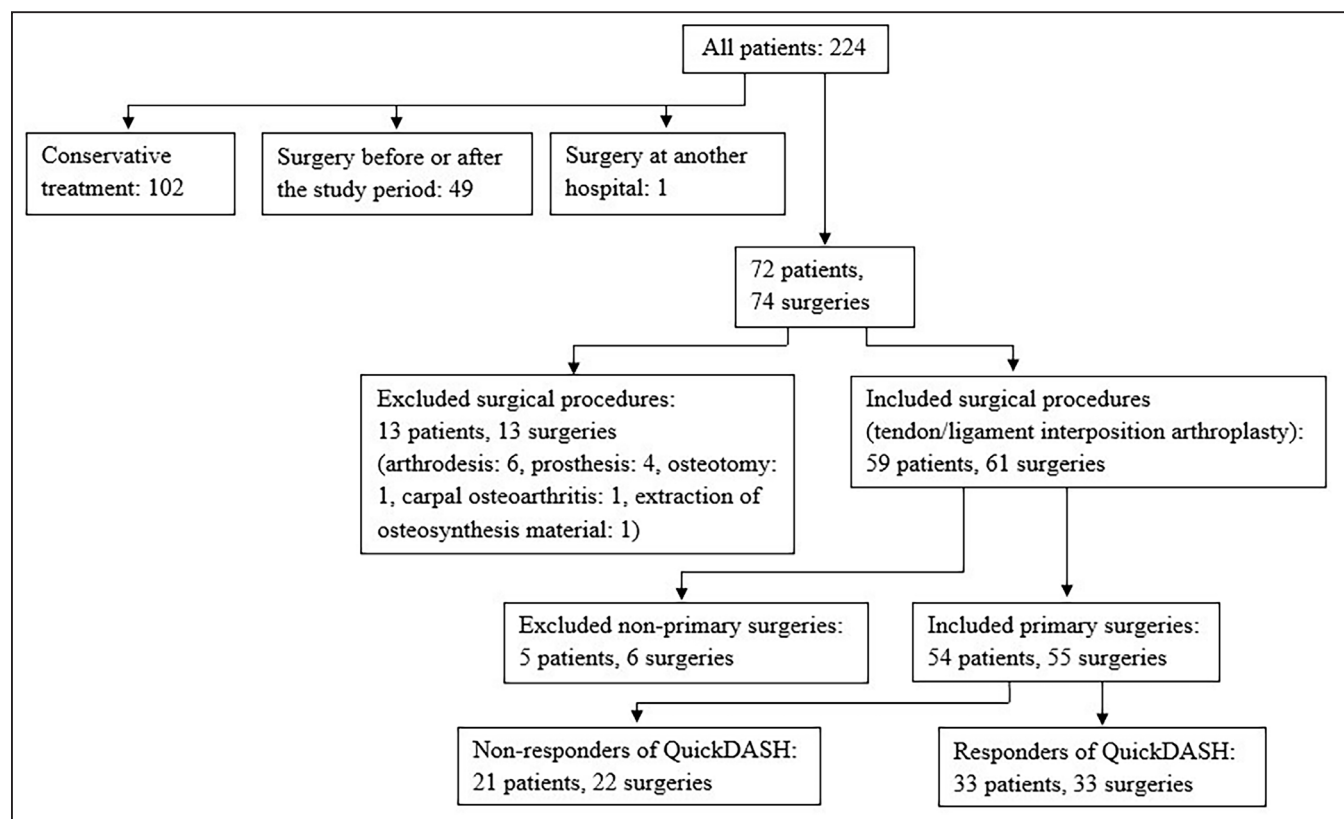
with age [1-5] and radiological and clinical findings do not always correlate [2].

A variety of conservative and surgical treatment options are available for treatment of OA of the CMC

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**Figure 1.** Flowchart of the study population.

1 joint [6-9]. When conservative treatment no longer relieves pain, and the inference with daily activities is substantial, surgery is an option [9-11].

We aimed to evaluate the results of primary surgical treatment with LRTI due to OA of the CMC 1 joint; particularly assessing the patients' pre- and post-operative symptoms [12,13], adverse effects, duration and costs for treatment.

## Patients and Methods

### Patients

All patients, who were admitted to our department due to OA of the CMC 1 joint from September 2009 to February 2011, were identified in the hospital registries (codes M150 and M18X according to ICD-10). A total of 224 patients were found, of whom 152 were discarded: 102 were treated conservatively, 49 had been through surgery before or after the study period, and one had been through surgery at another hospital. Thus, 72 surgically treated patients (74 surgeries) re-

mained for further analyses.

By reviewing the medical records, only primary surgeries, where LRTIs being the most used method, were included. Thirteen patients (13 surgeries) were excluded due to other surgical procedures: six arthrodesis, four prosthesis, one osteotomy, one surgery due to carpal OA and one removal of osteosynthesis material. Fifty-nine patients (61 surgeries), where LRTIs were performed, remained. Out of these, another five patients (six surgeries) were excluded because of non-primary surgeries. The study population consisted of 54 patients (one patient had surgery in both thumbs during the study period) and 55 surgeries (Figure 1).

### Questionnaire

According to departmental routines, all patients, who are registered for surgery, are asked to fill out a health declaration form and the QuickDASH questionnaire [12-14]. Patients are asked to fill out the questionnaire preoperatively and at one year after the

surgery. Of the 54 patients (i.e., 55 surgeries) documentation was available both pre- and postoperatively for 33 patients (i.e., 33 surgeries; responders); thus, a response rate of 61% and 60%, respectively. Nineteen patients (20 surgeries) had not answered the QuickDASH questionnaire at all, and two patients (two surgeries) had only answered preoperatively. Thus, 21 patients (22 surgeries) had missing QuickDASH documentation (i.e., non-responders).

### **Medical records**

The medical records of the 33 responders were reviewed. Basic information included age, sex, length and weight (i.e., Body Mass Index; BMI), dominant hand, the presence of other medical conditions, such as diabetes and hypertension, and smoking habits. Details about previous surgery to the hand and the presence of any other hand-related conditions were collected.

The surgeon's experience and the duration of the surgery were noted. We also noted if some patients had simultaneous surgery. Postoperative symptoms and duration of hospital stay were registered. Regarding postoperative symptoms, particular attention was given to pain, the mobility of the thumb, weakness, sensory in the innervation area of the radial nerve, and local symptoms related to scar.

The number of visits, related to the OA of the CMC 1 joint, to the professional team in the outpatient unit, was counted. The patients were followed up to one year postoperatively. For those 21 patients (22 surgeries; non-responders) who had missing QuickDASH documentation, medical records were reviewed similarly to characterize these patients for comparison.

### **Radiological classification**

Preoperative radiological staging of all 54 patients (55 surgeries) was performed (experienced radiologist unaware of the patients' symptoms and clinical signs) according to Eaton [15].

### **Calculation of costs**

Costs for treatment were calculated using prices given by Skåne University Hospital, Malmö, Sweden

2012 and converted according to the mean exchange rate 2012: US\$ 19 (€ 15) per minute of surgery, US\$ 175 (€ 132) per visit to the surgeon, US\$ 71 (€ 53) per visit to the rehabilitation unit or the nurses, and US\$ 482 (€ 364) for each day in the ward.

### **Statistical methods**

Values are presented as median (25<sup>th</sup>-75<sup>th</sup> percentiles) and nominal data as numbers (n) and percent (%). Chi-square test and Mann-Whitney test were used to detect any significant differences between different groups (independent samples). Wilcoxon signed rank test was used to detect differences between dependent samples. Spearman's correlation coefficient was used to analyze the association between observations. P-values <0.05 were considered to indicate statistical significance.

### **Ethics**

This is a quality control study why the the Swedish law regarding vetting the ethics of research involving humans (2004) is not mandatory. We have considered potential ethical problems with the study mainly regarding integrity and secrecy. We have thereby concluded that this report of our surgical results not entails any risks for the participating patients in accordance with similar published papers [16] and presented to the Regional Ethical Review Board (#2011/607). Chief of service at our department approved the quality control.

### **Results**

#### **Demographic and medical data of the study population**

Information about the 54 patients is given in Table I. The presence of any cardiovascular disease, diabetes mellitus, hypertension or hyperlipidemia was used as a general indicator of potentially increased surgical risks. No differences were found between the responders and non-responders of QuickDASH. Out of the 54 patients, 25 (46%) were still active in the labor market and needed a doctor's certificate for their sick leave.

#### **Hand-related data**

Data are based on 54 patients (55 surgeries) and all numbers represent only conditions affecting the

**Table 1.** Demographic and medical data of the study population, where osteoarthritis of the first carpometacarpal joint was surgically treated.

	All patients (n=54)	Responders QuickDASH <sup>a</sup> (n=33)	Non-responders QuickDASH <sup>b</sup> (n=21)	P-values
Sex (women)	47 (87%)	31 (94%)	16 (76%)	0.096
Age (years)	63 (58-68)	65 (58-70)	60 (54-68)	0.115
BMI (kg/m <sup>2</sup> )	26 (23-30) <sup>1</sup>	25 (23-30)	28 (26-29) <sup>2</sup>	0.135
Smoking	14 (26%)	9 (27%)	5 (24%)	1.000
Cigarettes/day	10 (6-14) <sup>3</sup>	12 (7-15) <sup>4</sup>	7 (4-10)	0.111
Diabetes mellitus	1 (2%)	1 (3%)	0 (0%)	-
Hypertension	22 (41%)	12 (36%)	10 (48%)	0.571
Hyperlipidaemia	15 (28%)	9 (27%)	6 (29%)	1.000
Cardiovascular risk <sup>c</sup>	29 (54%)	16 (49%)	13 (62%)	0.407

Values presented as median (25<sup>th</sup>-75<sup>th</sup> percentiles) and nominal data as numbers and percentages. P-values represent comparisons between responders and non-responders of QuickDASH. All p-values are not calculated due to a small number of subjects within groups. <sup>a</sup>QuickDASH both pre- and postoperatively, <sup>b</sup>QuickDASH only preoperatively or not at all, <sup>c</sup>Presence of cardiovascular disease, diabetes mellitus, hypertension or hyperlipidaemia, <sup>1</sup>n=53, <sup>2</sup>n=20, <sup>3</sup>n=13, <sup>4</sup>n=8.

**Table 2.** Hand-related data, information about the present surgery and radiological classification of the patients surgically treated due to osteoarthritis of the first carpometacarpal joint.

	All surgeries (n=55)	Responders QuickDASH <sup>a</sup> (n=33)	Non-responders QuickDASH <sup>b</sup> (n=22)	P-values
Previous surgery due to other hand conditions	16 (30%) <sup>1</sup>	7 (23%) <sup>2</sup>	9 (41%)	0.225
Other hand conditions <sup>c</sup>	29 (53%)	21 (64%)	8 (36%)	0.058
Surgery to dominating hand	29 (58%) <sup>3</sup>	20 (61%)	9 (53%) <sup>4</sup>	0.763
Duration of surgery (min)	66 (55-80)	66 (58-77)	67 (51-84)	0.922
Simultaneous surgery	11 (20%)	6 (18%)	5 (23%)	0.739
Radiological classification	n=49	n=30	n=19	
Radiological stage	3 (3-4)	3 (3-4)	3 (3-4)	0.253
Stage I	0 (0%)	0 (0%)	0 (0%)	-
Stage II	1 (2%)	1 (3%)	0 (0%)	-
Stage III	32 (65%)	21 (70%)	11 (58%)	-
Stage IV	16 (33%)	8 (27%)	8 (42%)	-

Only conditions affecting the same hand as the present surgery included. Values presented as median (25<sup>th</sup>-75<sup>th</sup> percentiles) and nominal data as numbers and percentages. All p-values are not calculated due to a small number of the subject within groups. <sup>a</sup>QuickDASH both pre- and postoperatively, <sup>b</sup>QuickDASH only preoperatively or not at all, <sup>c</sup>Other hand conditions present, in addition to osteoarthritis of the first carpometacarpal joint, at time of the present surgery, <sup>1</sup>n=53, <sup>2</sup>n=31, <sup>3</sup>n=50, <sup>4</sup>n=17.

same hand as the present surgery (Table II). In 16/53 (30%) surgeries, the patients had previous surgery due to other hand conditions than OA of the CMC 1 joint (missing data for two surgeries performed long ago). In 29/55 (53%) surgeries, the patients also suffered from other hand conditions. However, there were no differences between responders and non-responders of

QuickDASH.

### Surgical procedures

No differences were found regarding surgical details between the responders and non-responders of QuickDASH. In 11/55 (20%) surgeries, simultaneous surgeries due to other hand-related conditions were performed (three carpal tunnel syndromes, two trigger

fingers, two ligament injuries, one neuroma removal, one extirpation of osteophytes, one excision of skin lesion, and one MCP joint arthrodesis; Table II). Fifty-four surgeries were performed as inpatient surgeries and one as outpatient surgery. The median hospital stay of 54 in-patient surgeries was 2 (2-2) days. Fifty-one (93%) out of 55 surgeries were performed by a specialist in hand surgery.

### **Radiological classification**

Forty-nine (89%) out of 55 surgeries could be radiologically evaluated (Table II); in three cases the preoperative examinations were missing, in two cases the OA involved only the ST joint and thus the classification system was not applicable, and in one case both the CMC 1 and the ST joints had normal appearances. Among the remaining 49 surgeries, the median radiological stage was 3 (3-4).

### **The QuickDASH questionnaire**

A significant improvement in total QuickDASH scores (33 responders; 33 surgeries; Table III) was found [preoperative 52 (42-72) and postoperative 34 (13-51),  $p=0.0001$ ]. Five out of 33 patients increased their QuickDASH score and 1/33 surgeries reported no difference at one year. Two QuickDASH questions, although being non-specific but describe thumb activities, but differed pre- and postoperatively, are compared separately (Wilcoxon rank test) with awareness that number of scale steps does not reflect amount of improvement; open a tight or new jar [preoperative 4 (4-5) and postoperative 4 (3-5),  $p=0.007$ ] and using a knife to cut food [preoperative 3 (2-4) and postoperative 2 (1-3),  $p=0.02$ ]. The 33 surgeries were also separated into two groups: smokers and non-smokers, which did not differ in the outcome (Table III).

Figures for change between pre- and postoperative QuickDASH scores  $<8$  or  $\geq 8$  are given; i.e., indicating a minimal clinically important difference [17]. The total postoperative QuickDASH scores  $\leq 10$  or  $>10$  are presented to illustrate the overall function of the hand (normal value in population 10 [18], although

**Table 3.** Results of the QuickDASH questionnaire of the patients with QuickDASH answers both pre- and postoperatively (i.e., responders).

QuickDASH score	Number of surgeries in responders of QuickDASH (n=33)
Total score:	
Preoperative	52 (42-72)
Postoperative	34 (13-51) $p=0.0001$
Median change	18 (3-38)
Open a tight or new jar:	
Preoperative score	4 (4-5)
Postoperative score	4 (3-5) $p=0.007$
Using a knife to cut food:	
Preoperative score	3 (2-4)
Postoperative score	2 (1-3) $p=0.02$
Change in total score <sup>a</sup> :	
$<8$	11 (33%)
$\geq 8$	22 (67%)
Postoperative total score:	
$\leq 10$	7 (21%)
$>10$	26 (79%)
Preoperative total score:	
Smokers <sup>1</sup>	61 (54-73)
Non-smokers <sup>2</sup>	48 (39-70) $p=0.109$
Postoperative total score:	
Smokers <sup>1</sup>	48 (15-61)
Non-smokers <sup>2</sup>	33 (12-47) $p=0.322$

The two questions; open a tight or new jar and using a knife to cut food, presented as the patients' grading, 1-5 points for each question. Values presented as median (25<sup>th</sup>-75<sup>th</sup> percentiles) and nominal data as numbers and percentages. <sup>a</sup>Change between pre- and postoperative scores, <sup>1</sup>n=9, <sup>2</sup>n=24.

vary with factors as age, gender and population [19]). The surgeries are separated according to a change  $<8$  or  $\geq 8$  between pre- and postoperative results, and a total postoperative score  $\leq 10$  or  $>10$  (Table IV). Five (15%) out of 33 surgeries were not dismissed from outpatient care within one year. In the groups with a change in QuickDASH  $\geq 8$  or a total postoperative QuickDASH score  $\leq 10$ , there were significantly fewer visits in the rehabilitation unit than among the other patients.



**Table 4.** QuickDASH both pre- and postoperatively (i.e., in responders) and different factors related to the surgical outcome and the postoperative period in the outpatient unit.

Factor	Change <8 (n=11)	Change ≥8 (n=22)	Postoperative score ≤10 (n=7)	Postoperative score >10 (n=26)	All surgeries (n=33)
Sex (women)	10 (91%)	21 (96%)	7 (100%)	24 (92%)	31 (94%)
Age (years)	65 (56-71)	65 (59-68) p=0.948	65 (62-68)	65 (58-70) p=0.597	65 (58-70)
BMI (kg/m <sup>2</sup> )	26 (22-31)	24 (23-31) p=0.903	23 (22-24)	26 (23-31) p=0.186	25 (23-30)
Smoking	2 (18%)	7 (32%)	2 (29%)	7 (27%)	9 (27%)
Cardiovascular risk <sup>a</sup>	2 (18%)	14 (64%)	4 (57%)	12 (46%)	16 (49%)
Radiological stage	3 (3-4) <sup>1</sup>	3 (3-4) <sup>2</sup> p=0.693	3 (3-3) <sup>3</sup>	3 (3-4) <sup>4</sup> p=0.361	3 (3-4) <sup>5</sup>
Previous surgery <sup>b</sup>	4 (40%) <sup>6</sup>	3 (14%) <sup>2</sup>	1 (14%)	6 (25%) <sup>4</sup>	7 (23%) <sup>7</sup>
Other hand conditions <sup>c</sup>	7 (64%)	14 (64%)	4 (57%)	17 (65%)	21 (64%)
Simultaneous surgery	0 (0%)	6 (27%)	0 (0%)	6 (23%)	6 (18%)
Follow-up, duration (days) <sup>†</sup>	92 (59-153) <sup>8</sup>	122 (68-189) <sup>2</sup> p=0.405	102 (80-237)	112 (65-176) <sup>2</sup> p=0.717	111 (67-179) <sup>9</sup>
Number of visits <sup>††</sup> ;					
Surgeon	3 (2-5)	3 (2-4) p=0.465	3 (2-4)	3 (2-4) p=0.835	3 (2-4)
Nurse	1 (1-1)	1 (1-2) p=0.278	1 (1-2)	1 (1-2) p=0.730	1 (1-2)
Rehabilitation unit	5 (4-9)	4 (3-4) p=0.037	3 (1-4)	5 (3-6) p=0.018	4 (3-6)

Only conditions affecting the same hand as the present surgery included. Values presented as median (25<sup>th</sup>-75<sup>th</sup> percentiles) and nominal data as numbers and percentages. P-values represent comparisons between; postoperative change <8 and ≥8 and, postoperative total score ≤10 and >10. All p-values are not calculated due to a small number of subjects within groups.

<sup>a</sup>Presence of cardiovascular disease, diabetes mellitus, hypertension or hyperlipidaemia, <sup>b</sup>Other hand conditions, except osteoarthritis (OA) of the first carpometacarpal joint (CMC 1), <sup>c</sup>Other hand conditions present, in addition to OA of the CMC 1 joint, at time of the present surgery.

<sup>†</sup>Only patients concluded within one year, <sup>††</sup>Only the postoperative visits in the outpatient unit included, <sup>1</sup>n=9, <sup>2</sup>n=21, <sup>3</sup>n=6, <sup>4</sup>n=24, <sup>5</sup>n=30, <sup>6</sup>n=10, <sup>7</sup>n=31, <sup>8</sup>n=7, <sup>9</sup>n=28.

### The postoperative period

Pain, reduced ability to move the thumb and weakness were noted as symptoms, and sensory impairment in the innervation area of the radial nerve and various local symptoms in the scar area were noted as adverse effects. In 32/33 (97%) surgeries, symptoms or adverse effects were present up to one year. Out of 32 surgeries, 28 (88%) patients experienced reduced ability of thumb movement, 25 (78%) from pain, 15 (47%) from local symptoms in scar area, 14 (44%) from weakness in thumb and 9 (28%) from sensory impairment in the innervation area of radial nerve. One patient had a postoperative infection requiring treatment with antibiotics, and one patient was at risk of the shoulder-hand syndrome.

Twenty-eight (85%) of the 33 surgeries were dismissed from outpatient care within one year postoperatively (median interval to final postoperative visit 111 (67-179) days). In 19 (68%) out of these 28 surgeries, remaining symptoms or adverse effects were reported at the very last visit; i.e. 11/19 (58%) patients suffered from pain, 6 (32%) from reduced ability to move thumb, 4 (21%) from weakness in thumb, 2 (11%) from local symptoms in the scar area and 1 (5%) from sensory impairment in the innervation area of the radial nerve.

For the remaining nine surgeries also concluded within one year, one patient reported no symptoms or adverse effects during follow-up and eight reported the final postoperative visit to be the first symptom-free vis-

it. Hence, the hand function was perceived as normal.

Five (15%) out of 33 surgeries were not dismissed from outpatient care within one year, due to various remaining symptoms and problems (remaining high QuickDASH scores). Those patients firstly required further rehabilitation with conservative treatment, and two of them were eventually scheduled for additional surgical treatment beyond the present observation period.

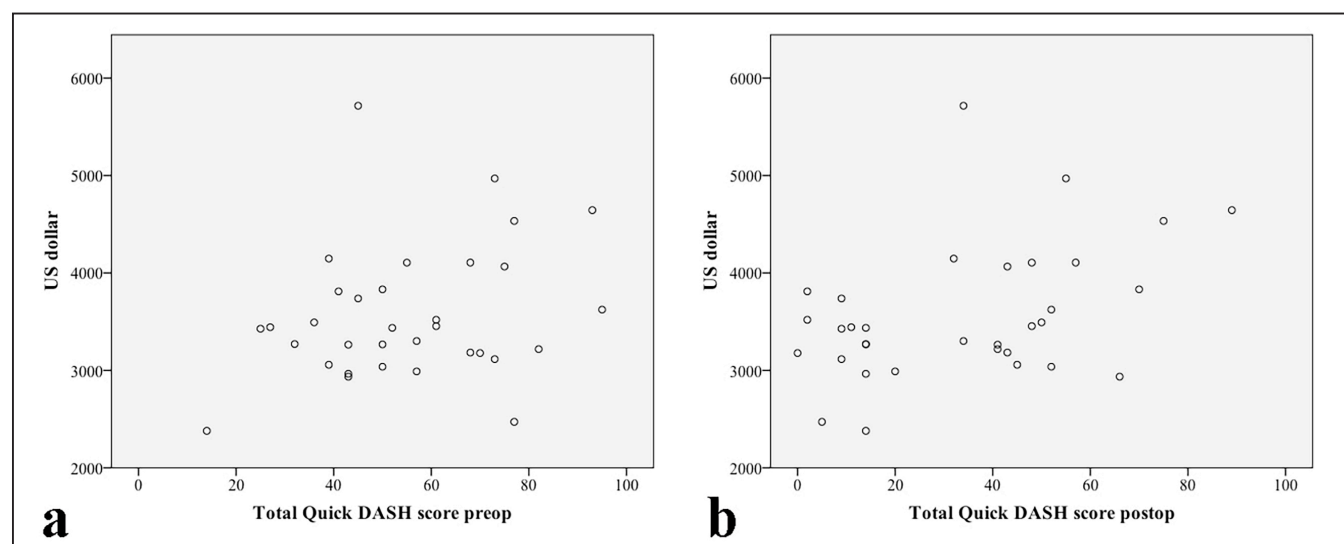
### Calculation of costs

The median number of visits for the 33 responders (33 surgeries) in the outpatient unit was 10 (9-14) with a median cost of US\$ 1267 (950-1668) [€ 956 (717-1258)] [surgeon 4 (3-7) visits, cost US\$ 701 (526-1226) [€ 529 (397-925)]; nurse 1 (1-2) visits, cost US\$ 71 (71-142) [€ 53 (53-107)]; rehabilitation unit 4 (3-6) visits, cost US\$ 283 (212-425) [€ 214 (160-320)]. The median duration of surgery was 66 (58-77) minutes with a median cost of US\$ 1271 (1107-1482) [€ 959 (835-1118)]. The median duration of hospital stay out of 33 in-patient surgeries was 2 (2-2) days with a median cost of US\$ 964 (723-964) [€ 727 (545-727)]. With all healthcare costs included, the median cost related to the treatment, was US\$ 3436 (3147-3949) [€ 2593 (2374-2979)].

Correlations analyses showed a significant fair correlation between the postoperative ( $r=0.352$ ,  $p=0.044$ ) QuickDASH score and costs for treatment (pre- and postoperative visits in the outpatient unit, duration of surgery and hospital stay). No significant correlation was found between the preoperative QuickDASH score and costs for treatment ( $r=0.206$ ,  $p=0.250$ ; Figure 2).

### Discussion

Our main findings were that patients, with women in majority [1,3-5], benefit from surgery, but residual problems were common even up to one year in our responders (60-61%; validated QuickDASH instrument; characteristics not different from non-responders [20-25]). General cardiovascular risk factors, where 29/54 (54%) suffered from at least one condition and with a slight overweight [26], should be considered when evaluating patient-reported outcomes. Smokers (26%), being more frequent than in the general Swedish population (prevalence 11%) [27], had higher DASH scores that non-smokers both pre- and postoperatively as reported after treatment of Dupuytren's contracture [16]. Several patients had a history of previous hand conditions and surgeries. Both previous surgical treatments and present hand conditions may influence the



**Figure 2.** QuickDASH scores and costs for treatment (pre- and postoperative visits in the outpatient unit, duration of surgery and hospital stay) of the responding 33 patients (33 surgeries) with QuickDASH both pre- and postoperatively. Correlations between pre- (a) and postoperative (b) scores and costs expressed in US \$ based on Spearman's correlation coefficient;  $r=0.206$ ,  $p=0.250$ ;  $r=0.352$ ,  $p=0.044$ , respectively.

result of the QuickDASH after LRTIs, which should be considered in future studies. No surgical method is superior to the other [10], although LRTI is associated with 12% more adverse effects [9].

The majority of our patients suffered from stage III OA (Eaton classification, which not correlates to the severity of symptoms [15,28]), and the present surgical technique is an applicable surgical option to treat this stage [9]. One problem in our classification was that all projections were not standardized, which may to some degree potentially influence our interpretations, but it did not have any significant importance for our conclusions.

Our patients had benefited from surgery, as after partial trapeziectomy and pyrocarbon interpositional arthroplasty [11], with significant improvement in QuickDASH scores, even in the two separate questions that we interpret to be related to the crucial function of the thumb [29-31]. Trapeziectomy, with or without reconstruction, is a difficult subject, where a variety of factors have to be judged, including psychosocial aspects [32]. A preoperative challenge is to differentiate those patients who will benefit from surgery from those who will not.

Another approach in using QuickDASH is to evaluate factors related to a total postoperative QuickDASH score of  $\leq 10$  [18], which gives an estimate of the actual function of the hand, although normative QuickDASH score varies depending on age, gender and population [19]. Most of the present patients had a postoperative score  $> 10$ , which may indicate that even though patients benefit from surgery, having a change in score  $\geq 8$ , the postoperative function of the hand is not equal to the function in a generally healthy population [18], even reflecting the relation between the QuickDASH score and age of the patients [19]. QuickDASH data were collected prospectively, but the other clinical data were collected by a retrospective approach, which is a limitation since such a collection is not completely standardized. Furthermore, the majority of responding patients suffered from symptoms and/or

adverse effects during the follow-up. Although the surgery is a routine procedure, the length of the postoperative treatment was rather extensive. Nineteen (68%) out of these 28 patients still suffered from symptoms or adverse effects at the final visit, mostly related to pain. There were significantly fewer visits to the rehabilitation unit in the responding patients with a change  $\geq 8$  and a postoperative score  $\leq 10$ , implying that patients experiencing greater postoperative disability as well as a minor change in QuickDASH score need more rehabilitation. Unfortunately, due to small numbers within various subgroups, it was not possible to statistically assess effects of possible risk factors, such as smoking and cardiovascular disease, or simultaneous surgery for remaining symptoms, which is a limitation.

A significant, but moderate, correlation was found between the postoperative score, and total costs, which are probably explained by a greater number of visits to the outpatient unit rather than by duration of surgery or hospital stay. Health care varies from country to country, and our calculations of costs are applicable only for countries with health care systems similar to that in Sweden. The median age of the patients was 63 (58-68) years, and 25/54 (46%) patients were still active in the labor market, which in turn affects actual costs for treatment. Costs related to sick leave need to be considered to achieve a complete understanding of total costs, but such information was not accessible.

### Conflict of interest statement

The authors have no conflicts of interest to declare.

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