ACR Open Rheumatology
Vol. 1, No. 8, October 2019, pp 507–515
DOI 10.1002/acr2.11062

American College of Rheumatology
Empowering Rheumatology Professionals

The Relation Between Disease Activity, Patient-Reported Outcomes, and Grip Force Over Time in Early Rheumatoid Arthritis

Maria Rydholm,[1] Ingegerd Wikström,[1] Sofia Hagel,[2] Lennart T. H. Jacobsson,[3] and Carl Turesson[1]

Objective. The objective of this study is to identify early predictors of future reduced grip force in patients with rheumatoid arthritis (RA) and to identify early predictors of grip force over time.

Methods. In a structured follow-up of an inception cohort of patients with early RA, average grip force values of the dominant hand were evaluated and compared with the expected based on age- and sex-specific reference values. Potential predictors of reduced grip force (less than 50% of expected) at 5 years were examined using logistic regression. Differences in percentage of expected grip force values over the study period and differences in change over time, by baseline disease parameters, were estimated using mixed linear-effects models.

Results. Among 200 patients with early RA, 44% had reduced grip force 5 years after diagnosis. Baseline characteristics that predicted reduced grip force at 5 years included high scores for the Health Assessment Questionnaire Disability Index (odds ratio 1.54 per SD; 95% confidence interval 1.13-2.11), high scores for pain and patient global assessment, and low grip force. C-reactive protein levels, the erythrocyte sedimentation rate, the 28-joint Disease Activity Score (DAS28), rheumatoid factor, anti–cyclic citrullinated peptide antibodies, joint counts, and synovitis of individual joints in the dominant upper extremity did not predict reduced grip force. Patients with baseline synovitis of the wrist or metacarpophalangeal joints or patients with a high DAS28 had lower estimated grip force at inclusion but also greater improvement of grip force over time.

Conclusion. Patient-reported outcomes predicted reduced grip strength 5 years after diagnosis. This underlines the prognostic importance of disability in early RA. Joint counts and synovitis in individual joints may change rapidly in early RA and appear to be less predictive of long-term hand function.

INTRODUCTION

Rheumatoid arthritis (RA) is characterized by polyarthritis and commonly affects the small distal joints of the hands and feet (1). Joint destruction begins early in some cases and then often progresses rapidly, in particular in the hands (2,3). Early prediction of a severe disease phenotype remains a challenge (4). Most studies of prognostic markers have examined their relation to joint destruction. Conventional radiographic investigation of the hands and feet is, since many years, the most widely used method to estimate joint damage over time in such patients (5–7). Baseline and persistent synovitis (8) and also inflammation measured using the multi-biomarker disease activity score (9) have been shown to predict progression of structural damage in RA. Rheumatoid factor (RF) and/or anti–cyclic citrullinated peptide (CCP) seropositivity, as well as an increased erythrocyte sedimentation rate (ESR) or increased C-reactive protein (CRP) levels, predicted rapid radiographic progression over 3 years (2) and 5 years (10). Initial joint damage progression during the first year of disease is a major predictor of later progressive joint damage (11).

Assessment of objective measures of function is important in the evaluation of patients with RA (12,13). Grip force measurement is regarded as a relevant parameter of hand function in patients with RA (1,6,13,14).

Patients with early RA have substantially reduced grip force compared with expected values, based on the general population (15). Grip force has a major impact on disability, in particular, in female patients with RA (16). Lower grip force in the dominant

Supported by The Swedish Research Council, The Swedish Rheumatism Association, Region Skåne, and Lund University.

[1]Maria Rydholm, OT, Ingegerd Wikström, OT, PhD, Carl Turesson, MD, PhD: Lund University and Skåne University Hospital, Malmö, Sweden; [2]Sofia Hagel, PT, PhD: Lund University and Skåne University Hospital, Lund, Sweden; [3]Lennart T. H. Jacobsson, MD, PhD: Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden, and Lund University, Malmö, Sweden.

No potential conflicts of interest relevant to this article were reported.

Address correspondence to Carl Turesson, MD, PhD, Department of Rheumatology, Skåne University Hospital, Jan Waldenströms gata 1B, 205 02 Malmö, Sweden. E-mail: carl.turesson@med.lu.se.

Submitted for publication April 16, 2019; accepted in revised form July 8, 2019.

SIGNIFICANCE & INNOVATIONS

- Disability and pain, but not markers of inflammation or autoantibodies, predict long-term reduction of grip force in patients with early RA.
- Extensive synovitis is associated with reduced grip force at RA diagnosis but also with greater improvement in grip force over 5 years.
- Predictors of long-term hand function in early RA are different from predictors of radiographic progression.

hand has been shown to be a predictor of subsequent economic impact of RA (17). Some improvement of grip force over time has been demonstrated in many patients (12,15,18–21), but impaired grip strength was still observed both 2 years (15,18) and 5 years after diagnosis (15,20) independently in patients who were in clinical remission and among those with limited self-reported pain or disability (15). Impaired grip force in early RA has been reported up to 8 years follow-up after diagnosis (22). In established disease, grip strength and overall muscle strength is further reduced with increasing age and RA duration (23). On the other hand, several studies have demonstrated that hand function can be improved by target interventions in RA (19,24–29). For example, a randomized controlled study showed that structured hand training in patients with RA is effective (19).

In cross-sectional studies, reduced grip force is associated with high disease activity and extensive joint involvement (18,30). However, there is a lack of studies on prediction of grip force. Risk factors for impaired hand function may be useful in the management of patients with early RA. The objectives of this study were 1) to identify early predictors of future reduced grip force in patients with RA and 2) to examine the relation between baseline disease parameters and grip force over time in early RA.

PATIENTS AND METHODS

Patients. An inception cohort of patients with early RA (symptom duration: 12 months or fewer), recruited in 1995-2005, was investigated. The patients were diagnosed with RA by a rheumatologist and fulfilled the 1987 American College of Rheumatology classification criteria for RA (31). The study included individuals from a defined area: the city of Malmö, Sweden (population of 260 000 in 2000). Patients were recruited from the rheumatology outpatient clinic of Malmö University Hospital, which was the only hospital serving the city, and from the four rheumatologists in private practice in Malmö. All patients gave their written informed consent to participate, and the study was approved by the Regional Ethical Review Board for Southern Sweden (Lund, Sweden).

Clinical assessment. Patients were managed according to usual care, with no prespecified protocol for pharmacotherapy or rehabilitation. In a structured follow-up program, all patients were examined by the same rheumatologist. Visits were scheduled at 6, 12, and 24 months as well as at 5 years after inclusion. By using a standardized protocol, individual joints were assessed as swollen or not swollen and tender or not tender, and standard 28-joint swollen joint counts (SJCs) and tender joint counts (TJCs) were obtained. Disability was assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI) (32). The Swedish validated translated version of the HAQ-DI (33) was used. Patient-reported pain and patient global assessment of disease activity were assessed using visual analogue scales (VAS) (scale: 0-100). Information on treatment was obtained as previously described (15). Blood samples were obtained at the visit when the joint assessment was performed (within 1 hour). CRP levels and the ESR were analyzed using standard methods at the Department of Clinical Chemistry, Malmö University Hospital.

Assessment of grip force. Grip force (measured in newtons) was measured by using the electronic instrument Grippit (AB Detektor). This was performed at the same visit as the joint assessment (within 1 hour). The patient was seated comfortably in a chair without armrests with the shoulder, arm, and hand in standard positions, as previously described (34). The other arm was resting on the table. Standardized instructions were given. When using this procedure, the test-retest scores for Grippit measures have been demonstrated to be high (34). The grip force was measured alternately in the dominant hand and the nondominant hand three times, and the mean of the three measurement values from each hand was used. Average values of the 10-second uninterrupted grip were obtained, as previously described (15). Average grip force values of the dominant hand at inclusion and at the 1-year and 5-year follow-up visits were compared with the expected based on age- and sex-specific reference values from a convenience sample from a cross-sectional study of volunteers in the region of Oslo, Norway (35). Grip force values for each patient were expressed as a percentage of the expected based on the reference values.

Statistics. Potential baseline predictors of reduced grip force (defined as less than 50% of the expected) at 5 years were examined using logistic regression analysis. In addition, the impact of baseline disease parameters on grip force over time was examined. Differences in the percentage of expected grip force values over the study period and differences in change over time by baseline disease parameters were estimated using mixed linear-effect models. The intercept corresponded to the estimated mean grip force at baseline based on the regression line. Presence versus absence of synovitis of individual joints or joint groups of the dominant arm and continuous disease severity measures (per SD) were included as covariates. Furthermore, patients in

each of the three higher quartiles of baseline disease activity (28-joint Disease Activity Score [DAS28]), disability (HAQ-DI), and pain (VAS) were compared with those in the lowest quartile. Quartiles of each of the subcomponents in the DAS28 (ie, SJC, TJC, ESR, and patient global assessment [VAS-global]) were compared in the same manner.

RESULTS

In an inception cohort of 233 patients with early RA, a subcohort of 200 patients (70% women, mean age of 59.8 years, 62% RF-positive, 56% anti–CCP2-positive, median symptom duration of 7 months) (Table 1) were observed for 5 years and had available

Table 1. Characteristics at inclusion of the early RA cohort

	Inclusion		
	All Patients With Grip Force Data[a]	Patients With Data on Grip Force at the 5-y Follow-up	5-y Follow-up
N	200	173	173
Female sex, % (n)	70 (140)	71 (123)	71 (123)
Age, mean (SD), y	59.8 (14.7)	60.4 (14.6)	64.6 (14.3)
Symptom duration at inclusion, median (IQR), mo	7 (5-10)	7 (5-10)	7 (5-10)
RF-positive at inclusion, % (n)	62 (125)	65 (113)	65 (113)
Anti–CCP-positive at inclusion, % (n)	56 (99)	59 (89)	59 (89)
DAS28 (0-10), mean (SD)	4.6 (1.4)	4.6 (1.4)	3.6 (1.4)
HAQ (0-3), mean (SD)	0.85 (0.63)	0.86 (0.63)	0.76 (0.66)
Patient global assessment (VAS: 0-100), mean (SD)	42 (26)	44 (27)	34 (25)
Pain (VAS: 0-100), mean (SD)	41 (27)	41 (26)	30 (24)
SJC (out of 28), mean (SD)	7.9 (5.0)	7.8 (5.0)	5.2 (4.9)
TJC (out of 28), mean (SD)	6.3 (6.4)	5.9 (6.0)	3.0 (5.1)
Methotrexate treatment, % (n)	54 (108)	54 (93)	61 (106)
Other DMARDs, % (n)	31 (62)	32 (56)	24 (42)
Glucocorticoid treatment, % (n)	40 (79)	37 (64)	30 (51)
CRP, median (IQR), mg/l	9 (<9-23.5)	<9 (<9-28)	<9 (<9-10)
ESR, median (IQR), mm/h	20.5 (10-42)	21 (11-44)	16 (10-25)
Synovitis on dominant side			
Shoulder, % (n)	7 (13)	8 (14)	1 (2)
Elbow, % (n)	8 (16)	9 (16)	4 (7)
Wrist, % (n)	64 (127)	64 (109)	34 (59)
≥1 MCP joint, % (n)	79 (156)	76 (130)	67 (116)
≥1 PIP joint, % (n)	53 (105)	53 (90)	26 (45)
No. of MCP joints, median (IQR)	2 (1-3)	2 (1-3)	1 (0-3)
No. of PIP joints, median (IQR)	1 (0-2)	1 (0-2)	0 (0-1)
Tenderness on dominant side			
Shoulder, % (n)	30 (60)	34 (57)	18 (32)
Elbow, % (n)	12 (23)	11 (18)	2 (4)
Wrist, % (n)	45 (88)	45 (76)	13 (23)
≥1 MCP joint, % (n)	54 (106)	49 (83)	30 (52)
≥1 PIP joint, % (n)	42 (82)	40 (68)	22 (39)
No. of MCP joints, median (IQR)	1 (0-2)	0 (0-2)	0 (0-1)
No. of PIP joints, median (IQR)	0 (0-2)	0 (0-2)	0 (0-0)

Abbreviation: CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IQR, interquartile range; MCP, metacarpophalangeal; PIP, proximal interphalangeal; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.
[a]Average values of the dominant hand at any time point.

Table 2. Baseline predictors of reduced grip force (<50% of expected; average grip force values of the dominant hand) at 5 years in the early rheumatoid arthritis cohort

	Odds Ratio	95% Confidence Interval
Female sex	1.79	0.90-3.55
RF-positive	0.76	0.41-1.43
Anti–CCP-positive	0.99	0.52-1.90
DAS28 (per SD)	1.16	0.85-1.57
HAQ (per SD)	1.54	1.13-2.11
Pain (VAS) (per SD)	1.36	1.00-1.86
Patient global assessment (VAS) (per SD)	1.41	1.03-1.92
SJC (out of 28) (per SD)	0.86	0.63-1.17
TJC (out of 28) (per SD)	1.11	0.80-1.54
ESR (per mm/h) (per SD)	0.96	0.71-1.29
CRP (≥9 mg vs <9 mg/l)	0.72	0.39-1.32
Grippit average score, dominant hand (% of predicted) (per SD)	0.41	0.27-0.62
Synovitis on dominant side		
Shoulder	1.29	0.43-3.87
Elbow	0.98	0.35-2.78
Wrist	0.99	0.53-1.86
≥1 MCP joint	0.95	0.47-1.95
≥1 PIP joint	0.94	0.51-1.71
No. of MCP joints (per joint)	0.94	0.76-1.17
No. of PIP joints (per joint)	1.02	0.82-1.26
Joint tenderness on dominant side		
Shoulder	1.22	0.64-2.31
Elbow	2.16	0.79-5.88
Wrist	1.40	0.76-2.57
≥1 MCP joint	1.68	0.91-3.09
≥1 PIP joint	1.10	0.60-2.05
No. of MCP joints (per joint)	1.08	0.89-1.30
No. of PIP joints (per joint)	1.10	0.60-2.05

Abbreviation: CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MCP, metacarpophalangeal; PIP, proximal interphalangeal; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

data on grip force. Most patients were started on methotrexate and/or other disease-modifying antirheumatic drugs (DMARDs) less than 1 year after symptom onset (Table 1). A total of 17% initiated treatment with a biologic DMARD within 5 years. Baseline characteristics of the patients included in the present study and the original cohort were similar (Supplementary Table 1) . The right hand was dominant in 187 patients (93.5%).

At inclusion, 53% had synovitis of one or more proximal interphalangeal (PIP) joint in the dominant hand, whereas synovitis of metacarpophalangeal (MCP) joints, wrist, elbow, and shoulder joints in the dominant extremity was observed in 79%, 64%, 8%, and 7%, respectively. Five years after diagnosis, 76 patients (44%) had reduced grip force (less than 50% of the expected). The mean value for the average grip force of the dominant hand increased from 40% of expected at baseline to 57% at the 5-year follow-up. There was also improvement in standard clinical disease measures (Table 1).

Baseline characteristics that predicted reduced grip force at 5 years included high HAQ-DI scores (odds ratio [OR] 1.54 per SD; 95% confidence interval [CI] 1.13-2.11) and high scores for pain (OR 1.36 per SD; 95% CI 1.00-1.86) and patient global assessment (OR 1.41 per SD; 95% CI 1.03-1.92), but laboratory markers of inflammation (CRP level and ESR), the DAS28, RF, anti-CCP levels, and 28-joint SJCs and TJCs were not predictive of reduced grip force (Table 2). Furthermore, baseline synovitis involvement of individual joints in the dominant upper extremity did not predict reduced grip force at 5 years (Table 2). The higher the baseline grip force (percentage of the expected value), the lower the risk of reduced grip force at 5 years (OR 0.41 per SD; 95% CI 0.27-0.62) (Table 2).

Table 3. Average grip force (% of expected value) over time (from baseline to 5 y), by joint involvement in early RA (mixed model analysis)

	Intercept (95% CI)	Estimated Mean Difference Over Time (95% CI)	Change/Year (95% CI)	Difference in Change/ Year (95% CI)
Swollen shoulder	42.5% (30.4% to 54.7%)	−3.7% (9.2% to −16.7%)	2.5% (0.5% to 4.5%)	−0.5% (−2.9% to 2.0%)
No swollen shoulder	45.6% (41.9% to 49.3%)	...	2.9% (2.2% to 3.6%)	...
Swollen elbow	39.2% (27.3% to 51.0%)	−6.0% (6.2% to −18.2%)	3.1% (1.2% to 5.0%)	0.2% (−2.0% to 2.4%)
No swollen elbow	45.6% (41.9% to 49.3%)	...	2.9% (2.2% to 3.6%)	...
Swollen wrist	40.6% (36.6% to 44.5%)	−9.3% (−2.5% to −16.2%)	3.5% (2.7% to 4.3%)	1.7% (0.4% to 3.0%)
No swollen wrist	53.1% (46.5% to 59.8%)	...	1.8% (0.8% to 2.8%)	...
≥1 swollen MCP joint	42.0% (38.2% to 45.8%)	−11.0% (−3.1% to −18.9%)	3.2% (2.5% to 4.0%)	1.5% (0 to 3.0%)
No swollen MCP joint	56.0% (47.4% to 64.5%)	...	1.7% (0.3% to 3.2%)	...
≥1 swollen PIP joint	44.2% (39.3% to 49.1%)	−0.9% (5.8% to −7.6%)	3.2% (2.3% to 4.0%)	0.5% (-0.8% to 1.8%)
No swollen PIP joint	46.1% (40.9% to 51.2%)	...	2.6% (1.7% to 3.6%)	...

Abbreviation: CI, confidence interval; MCP, metacarpophalangeal; PIP, proximal interphalangeal; RA, rheumatoid arthritis.

Baseline estimates of average grip force (percentage of the expected value) were lower in patients with synovitis of each of the individual joints or joint groups compared with the corresponding joint or joint group (Table 3). The greatest differences, with nonoverlapping CIs, were seen in those with one or more MCP joint and those with a swollen wrist (Table 3). Patients with one or more swollen MCP joint or with wrist synovitis had lower grip force over time, whereas there were no such differences for synovitis of the shoulder, elbow, or PIP joints (Table 3). Improvement of grip force was significantly greater in those with wrist or MCP synovitis compared with those without swelling in these joints. No such differences were observed for synovitis of other joints of the dominant arm (Table 3).

There were negative associations for disease severity parameters (ie, Health Assessment Questionnaire [HAQ], DAS28, VAS-pain, VAS-global, SJC, TJC, and ESR) at baseline with estimated baseline grip force and grip force over time (Table 4). Higher baseline HAQ score, DAS28, SJC, TJC, and ESR were also associated with significantly greater improvement in grip force over time, whereas there were no such associations for VAS-pain (estimated difference in change per year: 0.4% of the expected grip force per SD; 95% CI –0.3% to 1.0%) and VAS-global (Table 4).

Patients with baseline parameters in the three higher quartiles had significantly lower mean grip force values over time compared with patients in the lowest quartiles (Table 5). Patients in the highest quartile of the DAS28 had significantly greater improvement compared with patients in the lowest quartile (Table 5). By contrast, there was no difference in improvement for those in the highest quartiles of VAS-pain or the HAQ (Table 5) compared with those in the lowest quartiles. Mean grip force values at each follow-up visit by quartile of the DAS28, VAS-pain, and HAQ are illustrated in Figures 1A-C.

Patients with RA with baseline subcomponents of the DAS28 in the highest quartiles had lower mean grip force values over time compared with those in the lowest quartiles (Supplementary Table 2) . Patients in the highest quartiles of SJC, TJC, or ESR had significantly greater improvement in grip force compared with patients in the lowest quartile (Supplementary Table 2). There was

Table 4. Relation between baseline disease severity parameters and average grip force (dominant hand; % of expected value) over time (from baseline to 5 y) in early RA (mixed model analysis)

	Estimated Mean Difference at Baseline per SD (95% CI)	Estimated Mean Difference Over Time per SD (95% CI)	Difference in Change/ Year per SD (95% CI)
HAQ	−12.0% (−15.2% to −8.8%)	−10.7% (−13.7% to −7.8%)	0.7% (0.05% to 1.3%)
Pain (VAS)	−8.0% (−11.5% to −4.6%)	−7.4% (−10.6% to −4.1%)	0.4% (−0.3% to 1.0%)
Patient global assessment (VAS)	−8.5% (−11.9% to −5.1%)	−8.0% (−11.1% to −4.8%)	0.3% (−0.4% to 0.9%)
DAS28	−11.5% (−14.8% to −8.2%	−9.3% (−12.4% to −6.2%	1.2% (0.6% to 1.8%)
SJC (out of 28)	−8.1% (−11.7% to −4.6%)	−5.6% (−8.9% to −2.2%)	1.4% (0.7% to 2.0%)
TJC (out of 28)	−9.3% (−12.8% to −5.7%)	−7.4% (−10.8% to −4.1%)	1.0% (0.4% to 1.7%)
ESR (per mm/h)	−5.8% (−9.3% to −2.3%)	−4.5% (−7.7% to −1.2%)	0.7% (0.1% to 1.4%)

Abbreviation: CI, confidence interval; DAS28, 28-joint Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

Table 5. Relation of baseline patient-reported outcomes and disease activity with grip force (% of expected value) over time, by quartile

	Intercept (95% CI)	Estimated Mean Difference (95% CI)	Change/Year (95% CI)	Difference in Change/Year (95% CI)
DAS28				
Quartile I (0.8-3.6)	61.4% (53.4% to 69.4%)	Reference	1.3% (0.02% to 2.6%)	Reference
Quartile II (3.7-4.7)	48.2% (41.8% to 54.5%)	−10.7% (−2.0% to −19.4%)	2.6% (1.4% to 3.9%)	1.3% (−0.4% to 3.1%)
Quartile III (4.8-5.7)	41.3% (34.6% to 47.9%)	−16.7% (−7.9% to −25.5%)	3.1% (1.9% to 4.4%)	1.8% (0% to 3.6%)
Quartile IV (5.8-7.8)	29.6% (24.1% to 35.1%)	−25.9% (−17.2% to −34.6%)	4.4% (3.2% to 5.7%)	3.1% (1.4% to 4.9%)
VAS pain				
Quartile I (0-19)	59.4% (52.0% to 66.7%)	Reference	1.8% (0.5% to 3.1%)	Reference
Quartile II (20-39)	45.2% (37.6% to 52.9%)	−11.3% (−2.2% to −20.4%)	3.4% (2.0% to 4.7%)	1.5% (0.3% to 3.4%)
Quartile III (40-63)	34.7% (29.1% to 40.4%)	−20.8% (−12.2% to −29.5%)	3.9% (2.8% to 5.0%)	2.1% (0.4% to 3.8%)
Quartile IV (64-100)	41.0% (34.2% to 47.8%)	−17.4% (−8.6% to −26.3%)	2.3% (0.9% to 3.7%)	0.5% (−1.3% to 2.3%)
HAQ				
Quartile I (0-0.38)	62.2% (55.1% to 69.3%)	Reference	2.0% (0.8% to 3.2%)	Reference
Quartile II (0.39-0.75)	43.2% (36.2% to 50.1%)	−17.7% (−9.2% to −26.3%)	2.7% (1.4% to 4.0%)	0.7% (−1.1% to 2.5%)
Quartile III (0.80-1.25)	42.6% (36.8% to 48.4%)	−17.0% (−8.8% to −25.1%)	3.4% (2.2% to 4.6%)	1.4% (−0.3% to 3.1%)
Quartile IV (1.30-2.75)	28.8% (22.8% to 34.8%)	−30.6% (−22.0% to −39.2%)	3.5% (2.0% to 5.0%)	1.5% (−0.3% to 3.4%)

Abbreviation: CI, confidence interval; DAS28, 28-joint Disease Activity Score; HAQ, Health Assessment Questionnaire; VAS, visual analogue scale.

no such difference for those in the highest quartile of VAS-global (Supplementary Table 2).

DISCUSSION

In this study of patients with early RA, poor patient-reported outcome measures (PROMs) at baseline (ie, high HAQ-DI scores and high scores for pain and patient global assessment) predicted reduced grip force at 5 years. Seropositivity and the standard measures of disease activity were not predictive of reduced grip force. This contrasts with the well-documented association between these parameters and radiographic progression, which has also been demonstrated in this patient population (10). Possibly, the lack of association between traditional prognostic markers and long-term reduced grip force may reflect results of early intensive treatment, in particular, in patients with a severe early phenotype. However, a major proportion of the patients (44%) still had reduced grip force at 5 years. The results of this study underline the importance of using PROMs in the assessment of patients with RA, which is an important part of modern management (36).

Baseline synovitis involvement of individual joints in the dominant upper extremity did not predict reduced grip force at 5 years. As expected, the higher the baseline grip force (percentage of the expected value), the lower the risk of reduced grip force at 5 years.

Patients with synovitis of each of the individual upper extremity joints or joint groups had lower baseline estimates of average grip force (percentage of the expected value) compared with the corresponding joint or joint group. The greatest differences were seen in those with more than one 1 MCP joint and those with a swollen wrist. Over 5 years, patients with more than 1 swollen MCP joint or with wrist synovitis had lower grip force, whereas there was no such difference for synovitis of the shoulder, elbow, or PIP joints. Patients with wrist or MCP synovitis had significantly greater improvement of grip force during the follow-up compared with those without swelling in these joints.

Disease severity parameters at baseline were negatively associated with estimated baseline grip force and grip force over 5 years. Higher baseline levels of disease activity were also associated with greater improvement in grip force over 5 years, whereas there were no such associations for VAS-pain and VAS-global.

Again, this suggests that patients with poor PROMs in early RA are at increased risk of persistently impaired hand function. This is compatible with other studies that have demonstrated that poor PROMs predict long-term disability and low levels of physical activity (37). Underlying mechanisms may include poor coping strategies and activity limitation due to severe pain (38,39).

Structured analysis of coping strategies in patients with RA has demonstrated that evasive and emotive strategies are common but often not very effective and that, in particular, emotive strategies are frequently used in patients with severe pain (38). Ineffective coping strategies may further contribute to disability.

Pain in RA is multifactorial (40), often persistent over time (41), and a major predictor of general health perception (42). Particular interventions to improve function and health-related quality of life may be necessary in patients with early RA and severe pain. For the patient, severe pain and extensive disability is a warning sign that indicates increased risk of impaired long-term hand function. The study results indicate that patients with severe VAS for pain and global assessment (in the highest quartiles; VAS score of 64 or higher and 65 or higher, respectively) and severe disability (highest quartile; HAQ-DI score: 1.3 or higher) at diagnosis had particularly

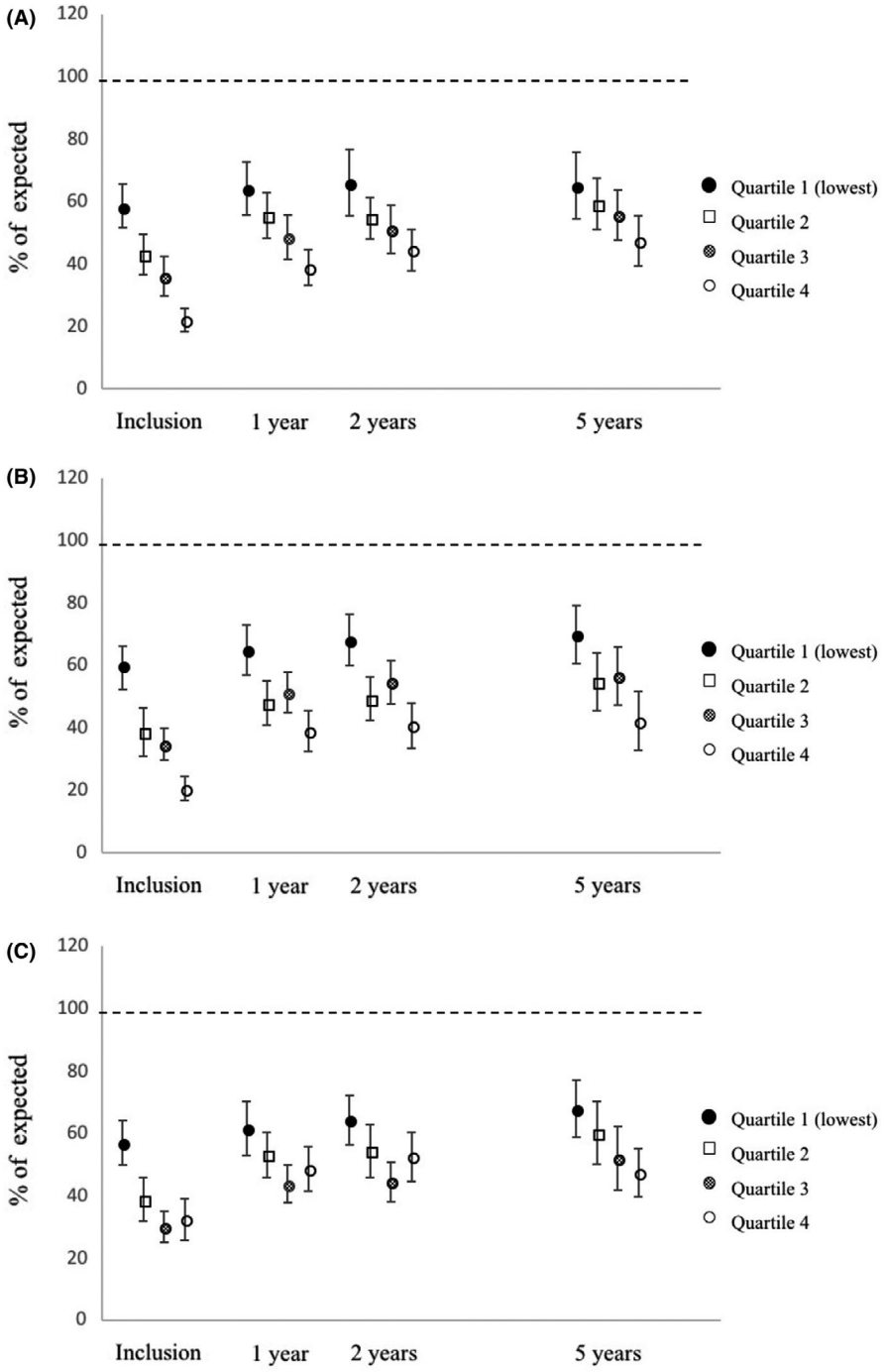

Figure 1. Average grip force (percentage of excepted; dominant hand) over time in patients with early rheumatoid arthritis (RA) by quartile of the 28-joint Disease Activity Score (DAS28), visual analogue scale (VAS) pain score, and Health Assessment Questionnaire (HAQ) score. Data are presented as mean values at each visit with 95% confidence intervals. **A**, Relation between baseline DAS28 and grip force from inclusion to the 5-year follow-up. **B**, Relation between baseline VAS pain and grip force from inclusion to the 5-year follow-up. **C**, Relation between baseline HAQ and grip force from inclusion to the 5-year follow-up.

reduced grip force, with limited improvement over time. It is very important for the rheumatology team to identify this category of patients early and initiate appropriate interventions with the purpose of improving grip force. It has been demonstrated that structured rehabilitation programs in RA may improve grip force (19,43) and reduce pain (19,44). Randomized controlled studies have shown that a combination of hand-strengthening and hand-mobilizing exercises for the distal upper extremity may give significant improvements in hand function (19,43). For example, in the Strengthening And stretching for Rheumatoid Arthritis of the Hand (SARAH) trial, a tailored hand-exercise program was shown to improve hand function in patients

with RA (19). For patients with RA with severe pain, particular coping strategies, such as mind or body techniques for managing pain, may be useful (45).

Limitations of the present study include the lack of a control group of individuals without RA evaluated at our unit. Like in a previous study (15), we used age- and sex-specific reference values from the literature, based on another study from Scandinavia (35), to calculate percentages of expected values of grip force for each individual. Based on this, we estimated the effect of other variables on age- and sex-standardized grip force.

Grip force was measured by several different observers. However, a standardized procedure was used by occupational therapists at our unit during the entire study period (34). All procedures were performed after 9:20 AM to limit the impact of morning stiffness.

PROMs were limited to standard VAS for pain and global assessment of disease activity and to the HAQ-DI; the latter is known to have floor effects in the assessment of disability (46). Newer PROMs, based on item response theory and computerized adaptive testing (46), were not available when this study was initiated. Finally, poor motivation may influence both PROMs and the Grippit measurement (47,48), but no assessment of motivation was available.

Management of RA changed continuously during the study period. The patients were included just before or shortly after the introduction of biologic DMARDs, and a limited number were treated with biologics before the 5-year follow-up. The study results may therefore not apply to patients managed according to a treat-to-target strategy (49), including ready access to biologic DMARDs.

Strengths of this study include the standardized joint assessment performed by the same physician in all cases using a structured protocol. Furthermore, standardized and established methods for assessment of grip force were used in accordance with the recommendations from the American Society of Hand Therapists (50). As recommended, the average of three assessments was used (50).

Because of the structured longitudinal follow-up of an inception cohort from a defined catchment area, selection bias is not a major issue in this study. Therefore, the results could be generalized to patients with RA seen in clinical practice.

Patients with a severe disease phenotype at baseline had particularly impaired grip force over the first 5 years after RA diagnosis. Patients with high initial disease activity experienced greater improvement in grip force, likely because of successful treatment. Poor patient-reported outcomes at baseline were associated with persistent impairment of grip strength. This underlines the prognostic importance of disability and related symptoms in early RA and suggests that targeted multi-professional interventions may be required in patients with a high HAQ score and severe pain (eg, those with a HAQ-DI score of 1.3 or higher or a VAS-pain score of 64 or higher). Joint counts and the presence of synovitis in individual joints may change rapidly in early RA and may appear to be less predictive of long-term hand function.

ACKNOWLEDGMENTS

In remembrance of Christina Book, MD, PhD, who initiated this project and performed a major part of the data collection. She passed away before the preparation of this manuscript.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual contact, and all authors approved the final version to be published. Dr. Turesson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Jacobsson, Turesson.
Acquisition of data. Rydholm, Wikstrom.
Analysis and interpretation of data. Rydholm, Hagel, Turesson.

REFERENCES

1. Bodur H, Yilmaz O, Keskin D. Hand disability and related variables in patients with rheumatoid arthritis. Rheumatol Int 2006;26:541–4.
2. Machold KP, Stamm TA, Nell VP, Pflugbeil S, Aletaha D, Steiner G, et al. Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease. Rheumatology (Oxford) 2007;46:342–9.
3. Lindqvist E, Jonsson K, Saxne T, Eberhardt K. Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis. Ann Rheum Dis 2003;62:611–6.
4. Bugatti S, Manzo A, Caporali R, Montecucco C. Assessment of synovitis to predict bone erosions in rheumatoid arthritis. Ther Adv Musculoskelet Dis 2012;4:235–44.
5. Krabben A, Huizinga TW, Mil AH. Biomarkers for radiographic progression in rheumatoid arthritis. Curr Pharm Des 2015;21:147–69.
6. Adams J, Burridge J, Mullee M, Hammond A, Cooper C. Correlation between upper limb functional ability and structural hand impairment in an early rheumatoid population. Clin Rehabil 2004;18:405–13.
7. Kyburz D, Finckh A. The importance of early treatment for the prognosis of rheumatoid arthritis. Swiss Med Wkly 2013;143:w13865.
8. Dougados M, Devauchelle-Pensec V, Ferlet JF, Jousse-Joulin S, D'Agostino MA, Backhaus M, et al. The ability of synovitis to predict structural damage in rheumatoid arthritis: a comparative study between clinical examination and ultrasound [published erratum appears in Ann Rheum Dis 2013;72:1270]. Ann Rheum Dis 2013;72:665–71.
9. Brahe CH, Ostergaard M, Johansen JS, Defranoux N, Wang X, Bolce R, et al. Predictive value of a multi-biomarker disease activity score for clinical remission and radiographic progression in patients with early rheumatoid arthritis: a post-hoc study of the OPERA trial. Scand J Rheumatol 2019;48:9–16.
10. Rydell E, Forslind K, Nilsson JA, Jacobsson LT, Turesson C. Smoking, body mass index, disease activity, and the risk of rapid radiographic progression in patients with early rheumatoid arthritis. Arthritis Res Ther 2018;20:82.
11. Tobon G, Saraux A, Lukas C, Gandjbakhch F, Gottenberg JE, Mariette X, et al. First-year radiographic progression as a predictor of further progression in early arthritis: results of a large national French cohort. Arthritis Care Res (Hoboken) 2013;65:1907–15.
12. Eberhardt K, Sandqvist G, Geborek P. Hand function tests are important and sensitive tools for assessment of treatment response in patients with rheumatoid arthritis. Scand J Rheumatol 2008;37:109–12.
13. Chandrasekaran B, Ghosh A, Prasad C, Krishnan K, Chandrasharma B. Age and anthropometric traits predict handgrip strength in healthy normals. J Hand Microsurg 2010;2:58–61.

14. Vliet Vlieland TP, van der Wijk TP, Jolie IM, Zwinderman AH, Hazes JM. Determinants of hand function in patients with rheumatoid arthritis. J Rheumatol 1996;23:835–40.
15. Rydholm M, Book C, Wikstrom I, Jacobsson L, Turesson C. Course of grip force impairment in patients with early rheumatoid arthritis over the first five years after diagnosis. Arthritis Care Res (Hoboken) 2018;70:491–8.
16. Hakkinen A, Kautiainen H, Hannonen P, Ylinen J, Makinen H, Sokka T. Muscle strength, pain, and disease activity explain individual subdimensions of the Health Assessment Questionnaire disability index, especially in women with rheumatoid arthritis. Ann Rheum Dis 2006;65:30–4.
17. Flipon E, Brazier M, Clavel G, Boumier P, Gayet A, Le Loet X, et al. Is it possible to identify early predictors of the future cost of chronic arthritis? The VErA project. Fundam Clin Pharmacol 2009;23:105–13.
18. Sheehy C, Gaffney K, Mukhtyar C. Standardized grip strength as an outcome measure in early rheumatoid arthritis. Scand J Rheumatol 2013;42:289–93.
19. Lamb SE, Williamson EM, Heine PJ, Adams J, Dosanjh S, Dritsaki M, et al. Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet 2015;385:421–9.
20. Bjork MA, Thyberg IS, Skogh T, Gerdle BU. Hand function and activity limitation according to health assessment questionnaire in patients with rheumatoid arthritis and healthy referents: 5-year followup of predictors of activity limitation (The Swedish TIRA Project). J Rheumatol 2007;34:296–302.
21. Bjork M, Thyberg I, Haglund L, Skogh T. Hand function in women and men with early rheumatoid arthritis. A prospective study over three years (the Swedish TIRA project). Scand J Rheumatol 2006;35:15–9.
22. Hallert E, Bjork M, Dahlstrom O, Skogh T, Thyberg I. Disease activity and disability in women and men with early rheumatoid arthritis (RA): an 8-year followup of a Swedish early RA project. Arthritis Care Res (Hoboken) 2012;64:1101–7.
23. Beenakker KG, Ling CH, Meskers CG, de Craen AJ, Stijnen T, Westendorp RG, et al. Patterns of muscle strength loss with age in the general population and patients with a chronic inflammatory state. Ageing Res Rev 2010;9:431–6.
24. Baillet A, Vaillant M, Guinot M, Juvin R, Gaudin P. Efficacy of resistance exercises in rheumatoid arthritis: meta-analysis of randomized controlled trials. Rheumatology (Oxford) 2012;51:519–27.
25. Brorsson S, Hilliges M, Sollerman C, Nilsdotter A. A six-week hand exercise programme improves strength and hand function in patients with rheumatoid arthritis. J Rehabil Med 2009;41:338–42.
26. Cima SR, Barone A, Porto JM, de Abreu DC. Strengthening exercises to improve hand strength and functionality in rheumatoid arthritis with hand deformities: a randomized, controlled trial. Rheumatol Int 2013;33:725–32.
27. Hall AM, Copsey B, Williams M, Srikesavan C, Lamb SE, Sarah Trial Team. Mediating effect of changes in hand impairments on hand function in patients with rheumatoid arthritis: exploring the mechanisms of an effective exercise program. Arthritis Care Res (Hoboken) 2017;69:982–8.
28. Hammond A, Prior Y. The effectiveness of home hand exercise programmes in rheumatoid arthritis: a systematic review. Br Med Bull 2016;119:49–62.
29. Williams MA, Williamson EM, Heine PJ, Nichols V, Glover MJ, Dritsaki M, et al. Strengthening and stretching for rheumatoid arthritis of the hand (SARAH): a randomised controlled trial and economic evaluation. Health Technol Assess 2015;19:1–222.
30. Van Lankveld WG, van 't Pad Bosch P, van de Putte L. Predictors of changes in observed dexterity during one year in patients with rheumatoid arthritis. Br J Rheumatol 1998;37:733–9.
31. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
32. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
33. Ekdahl C, Eberhardt K, Andersson SI, Svensson B. Assessing disability in patients with rheumatoid arthritis: use of a Swedish version of the Stanford Health Assessment Questionnaire. Scand J Rheumatol 1988;17:263–71.
34. Nordenskiold UM, Grimby G. Grip force in patients with rheumatoid arthritis and fibromyalgia and in healthy subjects: a study with the Grippit instrument. Scand J Rheumatol 1993;22:14–9.
35. Nilsen T, Hermann M, Eriksen CS, Dagfinrud H, Mowinckel P, Kjeken I. Grip force and pinch grip in an adult population: reference values and factors associated with grip force. Scand J Occup Ther 2012;19:288–96.
36. Buzatu C, Moots RJ. Measuring disease activity and response to treatment in rheumatoid arthritis. Expert Rev Clin Immunol 2019;15:135–45.
37. Malm K, Bergman S, Andersson M, Bremander A, BARFOT Study Group. Predictors of severe self-reported disability in RA in a long-term follow-up study. Disabil Rehabil 2015;37:686–91.
38. Mahat G. Perceived stressors and coping strategies among individuals with rheumatoid arthritis. J Adv Nurs 1997;25:1144–50.
39. Poh LW, He HG, Chan WC, Lee CS, Lahiri M, Mak A, et al. Experiences of patients with rheumatoid arthritis: a qualitative study. Clin Nurs Res 2017;26:373–93.
40. Sarzi-Puttini P, Salaffi F, di Franco M, Bazzichi L, Cassisi G, Casale R, et al. Pain in rheumatoid arthritis: a critical review. Reumatismo 2014;66:18–27.
41. Walsh DA, McWilliams DF. Mechanisms, impact and management of pain in rheumatoid arthritis. Nat Rev Rheumatol 2014;10:581–92.
42. Eurenius E, Brodin N, Lindblad S, Opava CH, PARA Study Group. Predicting physical activity and general health perception among patients with rheumatoid arthritis. J Rheumatol 2007;34:10–5.
43. Mathieux R, Marotte H, Battistini L, Sarrazin A, Berthier M, Miossec P. Early occupational therapy programme increases hand grip strength at 3 months: results from a randomised, blind, controlled study in early rheumatoid arthritis. Ann Rheum Dis 2009;68:400–3.
44. Dogu B, Sirzai H, Yilmaz F, Polat B, Kuran B. Effects of isotonic and isometric hand exercises on pain, hand functions, dexterity and quality of life in women with rheumatoid arthritis. Rheumatol Int 2013;33:2625–30.
45. Shariff F, Carter J, Dow C, Polley M, Salinas M, Ridge D. Mind and body management strategies for chronic pain and rheumatoid arthritis. Qual Health Res 2009;19:1037–49.
46. Fries J, Rose M, Krishnan E. The PROMIS of better outcome assessment: responsiveness, floor and ceiling effects, and Internet administration. J Rheumatol 2011;38:1759–64.
47. Porreca F, Navratilova E. Reward, motivation, and emotion of pain and its relief. Pain 2017;158 Suppl 1:S43–9.
48. Fishbain DA, Cutler R, Rosomoff HL, Rosomoff RS. Chronic pain disability exaggeration/malingering and submaximal effort research. Clin J Pain 1999;15:244–74.
49. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631–7.
50. Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil 1985;66:69–74.