Chapter 10

Predictors of stenosing tenosynovitis in the hand and hand-related activity limitations in patients with rheumatoid arthritis

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Abstract

Objectives. To identify early predictors of stenosing tenosynovitis in the hand and hand-related activity limitations in patients with rheumatoid arthritis (RA).

Design. A longitudinal study of an inception cohort.

Setting. A large outpatient clinic

Participants. Consecutive patients who attended the Early Arthritis Clinic for at least two years and fulfilled the ACR criteria for RA at baseline and/or at the 1-year follow-up were invited to participate until 200 patients were included.

Interventions. Not applicable.

Main Outcome Measures. Stenosing tenosynovitis, assessed by means of a standardised physical examination. Hand-related activity limitations assessed with the Disabilities of Arm, Shoulder and Hand questionnaire (DASH). A DASH score above the upper limit of the 95% range of the normative score was defined as abnormal. Prognostic factors: demographic and disease activity-related variables, radiographic damage, the Health Assessment Questionnaire (HAQ) total score and category scores at the 2-year follow-up.

Results. The mean ± standard deviation (SD) age was 59.7 ± 10.7 years, 75% were female. The mean ± SD time between the 2 year follow-up and the assessment of the dependent variables was 3.9 ± 2.7 years. Stenosing tenosynovitis was present in 33%. The median (interquartile range) DASH score was 26.7 (10.8-42.5); 30% were abnormal. Stenosing tenosynovitis was predicted by the HAQ category score for hand-use (HAQ-hand) at the 2-year follow-up (odds ratio [OR], 95% confidence interval [CI] = 2.3, 1.2-4.2). Hand-related activity limitations were predicted by the Disease Activity Score in 28 joints (OR, 95%CI = 1.8, 1.3-2.4) and HAQ-hand (OR, 95%CI = 2.4, 1.3-5.8) at the 2-year follow-up.

Conclusions. Stenosing tenosynovitis in patients with RA was predicted by HAQ-hand at the 2-year follow-up, and hand-related activity limitations were predicted by disease activity and HAQ-hand at the 2-year follow-up.

Introduction

Hand impairments and hand-related activity limitations[1] frequently occur in the early stages of rheumatoid arthritis (RA). At the time of diagnosis, involvement of the joints of the hand has been reported in 28 to 39%, and involvement of the joints of the wrist in 8% of patients, respectively.[2,3] Hand impairments have been found in 81% of RA patients who had a mean disease duration of 7.6 years.[4] Another study[5] reported that 90% of all patients with RA will develop hand impairments over time. In our rehabilitation center, a high prevalence of symptoms and hand and wrist impairments was found during 8 years of follow-up:[6] with 94% of the patients having at least one symptom (complaints of pain, stiffness, loss of muscle strength, paresthesia, complaints concerning a limited fist and a limited pinch grip, and joint deviation). In addition, 80% had at least one hand or wrist impairment (limited passive range of motion of the wrists or fingers, stenosing tenosynovitis, involvement of the first carpometacarpal joint, Z-deformity thumb, tendinitis of extensor tendons, or signs of carpal tunnel syndrome). The most common impairment was stenosing tenosynovitis, which was present in 33% of the patients. Data on the prevalence of activity limitations resulting from hand impairments in patients with RA are scarce. Although already present at the time of diagnosis, activity limitations can also occur later in the course of the disease.[7] In our centre, 30% of the patients had hand-related activity limitations.[6]

Hand impairments and hand-related activity limitations in patients with RA develop over time. Synovitis and tenosynovitis, which are the initial features, may cause destruction and instability of the joints, and an imbalance of muscle function. The impairments reinforce each other in such a way that they can eventually lead to serious hand deformities. To prevent these deformities and, more specifically, to prevent imbalance of muscle function, early detection and treatment of tenosynovitis seem mandatory. Knowledge about the symptoms and signs in early RA that can predict (enduring) hand impairments at a later stage is therefore a prerequisite. Hand-related activity limitations will frequently have a major impact on participation in daily activities such as household activities, work, hobbies and sports. If it was possible to predict the development of hand-related activity limitations, they could be prevented by means of early intervention.

There is little available information about the predictors of impairments and hand-related activity limitations in patients with early RA. Only 1 longitudinal study has reported that general activity limitation (ie, limitations in dressing and grooming, walking, hygiene) after 5 years of follow-up was predicted by grip force and general activity limitation at baseline.[8] and 2 cross-sectional studies have reported a correlation between reduced grip force and general activity limitations.[7,9] There is a complete lack of information concerning the prediction of stenosing tenosynovitis. Therefore, the objective of this study was to identify early predictors

of stenosing tenosynovitis in the hand and hand-related activity limitations in patients with RA.

Patients and Methods

Patients

The study population consisted of consecutive patients who attended an ongoing care and research cohort: the Early Arthritis Clinic (EAC) at the Jan van Breemen Institute, a large clinic for rheumatology and rehabilitation medicine in Amsterdam, in the Netherlands. Since 1995, newly referred patients are included in the EAC if they are $\geq$ 18 years of age, have peripheral arthritis in $\geq$ 2 joints and a symptom duration of $\leq$ 3 years prior to inclusion. Patients who have previously been treated with a disease-modifying anti-rheumatic drug (DMARD) and patients with spondylarthropathy, reactive arthritis, crystal-induced arthropathy, systemic lupus erythematosus, Sjögren's syndrome, or osteoarthritis are excluded. The baseline assessment consisted of an anamnesis and a physical examination by a rheumatologist and self-reported questionnaires. Patients subsequently were referred for follow-up assessments to the research nurses, and returned there annually for a physical examination, to fill in the self-reported questionnaires and for x-rays of hands and feet. The baseline and follow-up data obtained from the EAC were stored in an electronical database.

The inclusion criteria for our present study were: EAC patients who fulfilled the American College of Rheumatology (ACR) criteria for RA at baseline and/or one year after inclusion in the EAC, and at least two or more years of follow-up in this cohort. At least two years of follow up was considered necessary to establish adequate pharmacological therapy. All patients who were included had an appointment with the rehabilitation physician at the Department of Rehabilitation Medicine once for one additional examination for the present study. Recruitment for this additional examination started in December 2005 and continued until a total of 200 patients had been included in November 2008. Thus at the time of the additional examination the length of time that the patients were in the EAC ranged from 2 years (patients included in the EAC in 2003 and examined in 2005) to 13 years (for patients included in 1995 and examined in 2008). A schematic view of the research design is shown in Figure 1. The local Medical Ethics Committee approved the study protocol, and all patients gave written informed consent.

Measurements

Disease information

Data on demographics, symptom duration, DAS28[10] and functional status (the Dutch version of the HAQ)[11,12] were collected at the baseline examination by the rheumatologist, and during

the follow-ups by the research nurses. The laboratory assessments included erythrocyte sedimentation rate, CRP, IgM-RF and ACPA, as measured by antibodies to cyclic citrullinated peptide.
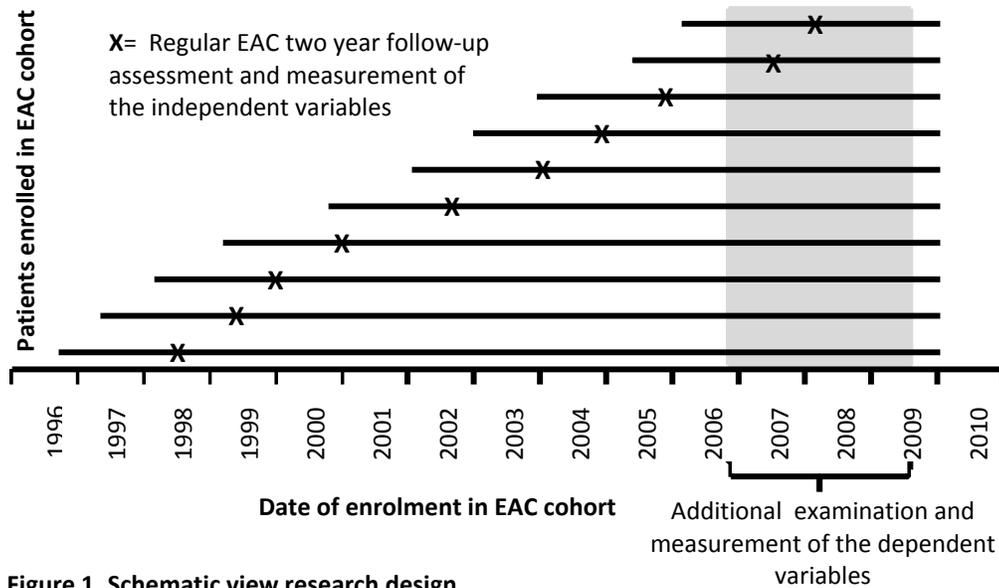

Figure 1. Schematic view research design

Dependent variables

Stenosing tenosynovitis. Stenosing tenosynovitis was assessed by two rehabilitation physicians who were blinded to each other (A.F.H. and N.C.H.) by means of a standardised physical examination during the additional examination for this study. Stenosing tenosynovitis was graded according to the ASSiST,[13] which has recently been developed. It has good inter-rater reliability (kappa=0.72) and comprises the following grades:

- Grade 0: Normal tendon-gliding.
- Grade 1: A palpable nodule or crepitation, with a normal active range of motion.
- Grade 2: A modified motion pattern caused by changed tendon-gliding (in a perceptible click, or a reduced tempo of active flexion), in combination with a full active range of motion.
- Grade 3: A restriction in active range of motion due to a tendon blockade under the pulleys or within the tendon sheath.

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Stenosing tenosynovitis was considered to be present if the ASSiST classification was grade 2 or higher, which is considered to be an indication for further conservative or surgical treatment.

Hand-related activity limitations. Hand-related activity limitations were assessed with the DASH during the additional examination for this study. The DASH is a 30-item questionnaire with 5 answer categories. The summed score is transformed to a standardised score (0–100), with higher scores indicating more limitations. It has been found to be valid and reliable in patients with RA.[14]

In our study, hand-related activity limitations were considered to be present if the DASH was classified as abnormal (ie, a DASH score above the normative mean DASH score plus twice the SD). The normative mean $\pm$ SD DASH for the general population is 10.1 $\pm$ 14.7,[15] so our definition of an abnormal DASH was 39.5 or higher.

Independent variables

Data from the 2-year follow-up of each participating EAC patient were used to predict the presence of stenosing tenosynovitis and hand-related activity limitations. Predictors were assessed at the 2-year follow-up because a stable state of medication-induced low disease activity is assumed to be reached at that time in most patients. Potential predictors were:

- Demographic variables: sex (female, yes or no) and age.
- Variables related to disease activity; DAS28, number of tender joints in the hand, number of swollen joints in the hand.
- Laboratory variables; CRP, IgM-RF (positive, yes or no) and ACPA (positive, yes or no).
- Variables related to functional status: HAQ total score and the HAQ category score for grip (HAQ-hand), which is an indicator of difficulty with use of the hands (Are you able to: Open car doors? Open jars which have previously been opened? Turn taps on and off? [Any difficulty with use of the hands, yes or no]).
- Variables related to radiographic damage; presence of erosions (a minimum a score of $\geq$1 according to the SHS, yes or no) or the presence of joint-space narrowing (a minimum score of $\geq$1 according to the SHS, yes or no) in metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints ,and the total SHS.[16]

All predictors were used as continuous variables unless stated otherwise.

Statistical analyses

All independent variables were univariately tested for both stenosing tenosynovitis and hand-related activity limitations by using logistic regression analysis. Variables with a *P* value less than 0.20 were added to the regression model that was used to predict stenosing tenosynovitis or hand-related activity limitations. If more than one of the variables was

related to functional status (ie HAQ total score and HAQ-hand had *P* values <0.20 only the 1 variable with the lowest *P* value was added. The same procedure was followed for variables related to radiographic damage. A backward logistic regression analysis was performed to predict: 1) the presence of stenosing tenosynovitis in the hands, and 2) the presence of hand-related activity limitations.

Backward logistic regression eliminates non-significant variables from the model in order to achieve the best, and simplest and best-fitting model with which to predict the dependent variable. The *P* value cut-off was 0.05. When DAS28 appears to be a predictor, the risk will be compared to the risk with a DAS28 of 2.59, which is just below the threshold defined as remission (DAS28 <2.6).[17] The regression model was corrected for disease duration, in order to obtain results independent of the varying duration of the disease among the patients. For both models the ROC of the predicted probabilities values was plotted, and the area under the curve was calculated. Statistical analyses were performed with SPSS 16.0 software (SPSS Institute Inc., Cary, NC, USA).

RESULTS

Patients

A total of 366 patients were invited to participate, but 166 patients were unwilling to participate after receiving an invitation for the assessment. The reasons were given for non-participation were logistic problems (19%), no specific reason (51%), or no hand symptoms (2%); 28% did not give any reason. The characteristics of the participants and the non-participants are presented in table 1. The 2 groups were comparable with regard to sex, marital status, mean disease duration, IgM-RF positivity, ACPA positivity, and SHS, DAS28 and HAQ scores. The participants were significantly older, on average, than the non-participants, and they also tended to have a higher DAS28.

Table 1. Patient characteristics at the additional examination

Characteristic	Participants	Non-participants	p †
	n=200	n=166	
Female, %	75	68	0.42
Age, mean ± SD	59.7 ± 10.7	55.8 ± 13.8	0.01
Marital status			0.72
Married/living together,%	67	71	
Single/divorced, %	23	21	
Widow(er), %	5	7	
Unknown	5	1	
Disease duration, years mean ± SD	5.9 ±2.7	5.4 ±3.2	0.12
IgM-RF positive, %	48	48	1.00
ACPA positive, %	58	60	0.76
SHS, median (IQR)	6 (0-25)	4 (0-11)	0.29
DAS28, mean ± SD	3.12 ± 1.50	2.82 ± 1.24	0.06
HAQ, median (IQR)	0.75 (0.13-1.25)	0.75 (0.13-0.88)	1.00

SD = Standard Deviation; IgM-RF= IgM rheumatoid factor ; ACPA = antibodies to anti-cyclic citrullinated peptide; SHS= Sharp-Van der Heijde score; IQR = Interquartile range; DAS28 = Disease Activity Score of 28 joints; HAQ = Health Assessment Questionnaire, † P-values were calculated to assess significant differences in characteristics between participants and non-participants. Variables with a normal Gaussian distribution were tested with the Student's t-test, variables not normally distributed with the Mann-Whitney U-test, and categorical variables with the χ2 test

Stenosing Tenosynovitis, Hand-related Activity Limitiations, and Potential Predictors

Stenosing tenosynovitis, hand-related activity limitations and potential predictors
The values of the potential predictors of stenosing tenosynovitis or hand-related activity limitations are summarised in Table 2. The mean ± SD disease duration from baseline was 5.9±2.7 years (the disease duration is equivalent to the follow-up duration). Therefore, the average time between the 2-year follow-up and the assessment of the dependent variables was 3.9±2.7 years.

Table 2. Values of dependent and independent variables

Variable	Value
Dependent variables at the additional examination (mean [SD] 5.9 [2.7] years of follow-up)	
stenosing tenosynovitis ≥ grade II, %	33
hand-related activity limitations, %	30
Independent variables (2-year follow-up)	
Age, years mean ± SD	61.7 ± 10.7
DAS28, mean ± SD	3.12 ± 1.30
CRP, mg/l median (IQR)	4 (2-10)
Number of tender hand/wrist joints, median (IQR)	0 (0-3)
Number of swollen hand/wrist joints, median (IQR)	1 (1-2)
IgM-RF positive, %	35
ACPA positive, %	47
HAQ total score, median (IQR)	0.63 (0.00-1.00)
HAQ-hand, presence of any difficulty with grip, %	44
Erosions MCP and PIP, presence of erosions in at least one joint, %	23
Joint-space narrowing MCP and PIP, %	16
SHS, median (IQR)	1 (0-9)

SD = Standard Deviation; DAS 28 = Disease Activity Score of 28 joints; CRP= c-reactive protein; IQR = Interquartile range; IgM-RF = IgM rheumatoid factor; ACPA = antibodies to anti-cyclic citrullinated peptide; HAQ = Health Assessment Questionnaire; HAQ-hand = Health Assessment Questionnaire, sub-scale regarding the use of hands; MCP = metacarpophalangeal joint; PIP = proximal interphalangeal joints; SHS= Sharp-Van der Heijde Score.

Predictors of stenosing tenosynovitis

Table 3 shows the logistic regression model used to predict stenosing tenosynovitis. The analysis was corrected for disease duration. The only variable which had a P value less than 0.20, and was added to the model, was HAQ-hand: stenosing tenosynovitis was predicted by HAQ-hand at the 2-year follow-up (OR, 95% CI, 2.3, 1.2-4.2). The ROC of the predicted probabilities values of this model is shown figure 2. The area under the curve is 0.62 (95% CI: 0.53-0.70).

Table 3. Predictors of stenosing tenosynovitis

Variables in model	OR (95%CI)	p
HAQ-hand	2.3 (1.2-4.2)	<0.001
Disease duration*	Corrected for	

OR = odds ratio; CI = confidence interval; HAQ-hand = Health Assessment Questionnaire, sub-scale regarding the use of hands. *The model is corrected for disease duration in order to obtain results independent of follow-up duration.

Patients who reported any difficulty with the use of their hands (HAQ-hand) at the 2-year follow-up had a 2.3 times higher risk of showing clinically relevant signs of stenosing

tenosynovitis later on in the course of the disease compared to patients without any difficulty with the use of their hands. Up to 44% of the study population had difficulties with the use of their hands according to the HAQ-hand at the 2-year follow-up.

Predictors of hand-related activity limitations

Table 4 shows the logistic regression model used to predict hand-related activity limitations, defined as a DASH score above 39.5. The analysis was corrected for disease duration. The variables added to the model (P<0.20) were DAS28, number of tender joints in the hand, and HAQ-hand. The number of tender joints was eliminated because it did not reach significance, meaning that it did not contribute to the best, simplest and best-fitting prediction model.

Hand-related activity limitations were predicted by the DAS28 (OR, 1.8 95% CI, 1.3-2.4) and by the HAQ-hand (OR, 2.7 95% CI, 1.3-5.8) at the 2-year follow-up. The ROC of the predicted probabilities values of this model is shown figure 2. The area under the curve is 0.78 (95% CI, 0.71-0.85).

Table 4. Predictors of hand-related activity limitations

Variables in model	OR (95%CI)	p
DAS28	1.8 (1.3-2.4)	<0.001
Tender joints hand[#]		0.55
HAQ-hand	2.7 (1.3-5.8)	0.01
Disease duration*	Corrected for	

OR = odds ratio; CI = confidence interval; DAS 28 = Disease Activity Score of 28 joints; HAQ-hand = Health Assessment Questionnaire, sub-scale score regarding the use of hands. [#]This variable was eliminated from the model. * The model is corrected for disease duration in order to obtain results independent of follow-up duration.

The OR of 1.8 is based on a increase in DAS28 of 1.00 points. This risk will increase exponentially with a higher DAS28. The mean DAS28 at the 2-year follow-up was 3.14, a 0.55 higher DAS28 compared to patients with a DAS28 of 2.59, which is just below the threshold defined as remission. This implies a $1.8^{0.55}=1.4$ times higher risk of hand-related activity limitations, compared to those patients with a DAS28 just below the remission threshold. In addition to the DAS28, the HAQ-hand gives a 2.7 times higher risk of hand-related activity limitations. Up to 44% of the study population had HAQ-hand at the 2-year follow-up. The combined predictors (a 1.4 times higher risk for mean DAS28 and presence of HAQ-hand [OR, 2.7] at the 2-year follow-up), can result in a 3.8 (1.4*2.7= 3.8) times higher risk of hand-related activity limitations in a later stage of the disease.
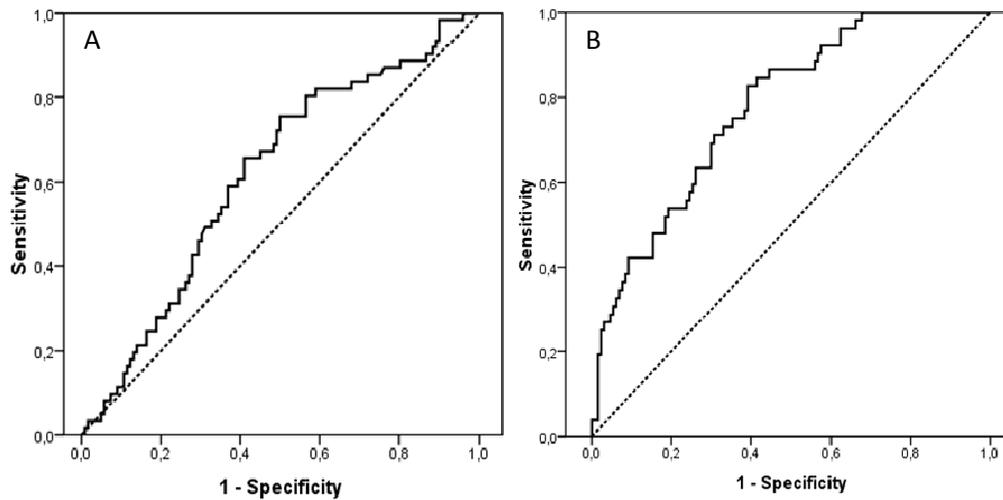
Figure 2 ROC curves for the predicted probabilities values of the prediction models. ROC curves for the predicted probabilities values for A) the model for Stenosing Tenosynovits and B) the model for hand-related activity limitations

Discussion

The aim of the present study was to identify early predictors of stenosing tenosynovitis in the hand and hand-related activity limitations in patients with RA.

We found that stenosing tenosynovitis was the most frequently observed impairment during an 8-year follow-up of RA patients6. The present results show that stenosing tenosynovitis, defined as an ASSiST 13 classification of grade 2 or higher, was predicted by the presence of the HAQ-hand at the 2-year follow-up.

Hand-related activity limitations, defined as a DASH score above the normative score plus twice the SD, were present in 30% of the patients, after a mean disease duration of almost 6 years. These hand-related activity limitations were predicted by a high DAS28 and the presence of HAQ-hand at the 2-year follow-up. Thus, patients with a greater disease activity at the 2-year follow-up have a worse prognosis with regard to hand-related activity limitations. Furthermore, once hand-related activity limitations are present (as measured with the HAQ), these limitations will remain present (as measured with the DASH). This is in agreement with a study which reported that hand function, after an initial improvement, was still greatly affected during the 3 years of follow-up 7. A correlation between grip force and general activity limitation at 3 years of follow-up was found in two studies.[7,9] One previous study8 reported that general activity limitation was predicted by grip force at baseline. To our knowledge, no research on the predictors of hand-related activity limitations has yet been carried out.

These findings are surprising, because the DAS28 and HAQ data, including HAQ-hand, are collected annually before the patient visits the physician, and are taken into account in the pharmacological treatment. This means that, even with optimal pharmacological treatment,

the threat of continuing deterioration of the hand will remain. Therefore, it indicates that patients with a high DAS28 and HAQ-hand need more than the current pharmacological treatment. Possible interventions for these patients are education on hand-use, the prescription of exercises, local corticosteroid injections, splinting, or even surgery.

Study Limitations

Although there was a high percentage of non-participants, we believe that our study population is representative for the total group of RA patients in our EAC cohort. The mean age of the participants was higher than the mean age of the total cohort, and they had a trend towards a slightly higher DAS28 score. If there might be a selection bias, this might have led to an over-estimation of the prevalence of stenosing tenosynovitis and hand-related activity limitations. However, the distribution of radiographic joint damage and the HAQ findings were the same in both groups.

Conclusion

In conclusion, in this study population of patients with RA, representative for all RA patients in the EAC, difficulty with use of the hands at the 2-year follow-up was the strongest predictor of stenosing tenosynovitis later in the course of the disease (ie after a mean + SD of 3.9+2.7 years of follow-up). The disease activity score, independent of difficulty with use of the hands at the 2-year follow-up, predicted hand-related activity limitations later in the course of the disease. Therefore, physicians should be aware of the DAS28 and the HAQ, and especially the HAQ-hand sub-scale, after a 2-year disease duration, so that other forms of intervention can be combined with the pharmacological treatment in an early stage.

Competing interests
The authors declare that they have no competing interests.

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