Early detection of patients at risk for rheumatoid arthritis

- a challenge for primary and secondary care -

Celina Alves

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Early detection of patients at risk for rheumatoid arthritis - a challenge for primary and secondary care -

Vroege herkenning van patiënten met een risico op reumatoïde artritis
- een uitdaging voor eerste en tweede lijn -

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CHAPTER One

General introduction

Rheumatoid Arthritis and the need for early recognition

Rheumatoid arthritis (RA) is a systemic auto-immune disease mainly characterized by articular manifestations [1]. Patients present initially with synovitis and joint damage, while extra-articular manifestations such as vasculitis, pleuritis and pericarditis are manifestations of severe or longstanding disease [1,2]. The prevalence of RA is approximately 1% [2]. It affects most patients in the fifth decade of life with females more affected than males [2]. The etiopathogenesis is not fully understood. Genetic, epigenetic and environmental factors seem to play a role [3,4].

Before the articular manifestations other features of RA can already be present. Nielen et al showed in a retrospective cohort of RA patient that donated blood that 49% of the patients were positive for anti-citrullinated protein antibody's (ACPA's) and rheumatoid factor (RF) up to 15 years before onset of symptoms [5]. This suggests that the disease develops in different stages which was recently depicted by Hazes and Luime [6,7]. They illustrated RA as stages of plant growth, see figure 1. In the pre-articular phase, all the genetic potential for the development of RA is present, but there are no signs or symptoms of disease. This stage can than develop into an arthralgia phase in which clinically objective synovitis is still not present. In the first clinical phase, symptoms and signs of synovitis indicate the presence of inflammatory arthritis but the form of arthritis is not classifiable and the arthritis is hardly discernable from other inflammatory rheumatic diseases. In the next clinical phase, the disease develops and shows more features of its definite form, and in the third clinical phase the arthritis is fully classifiable as RA [6].

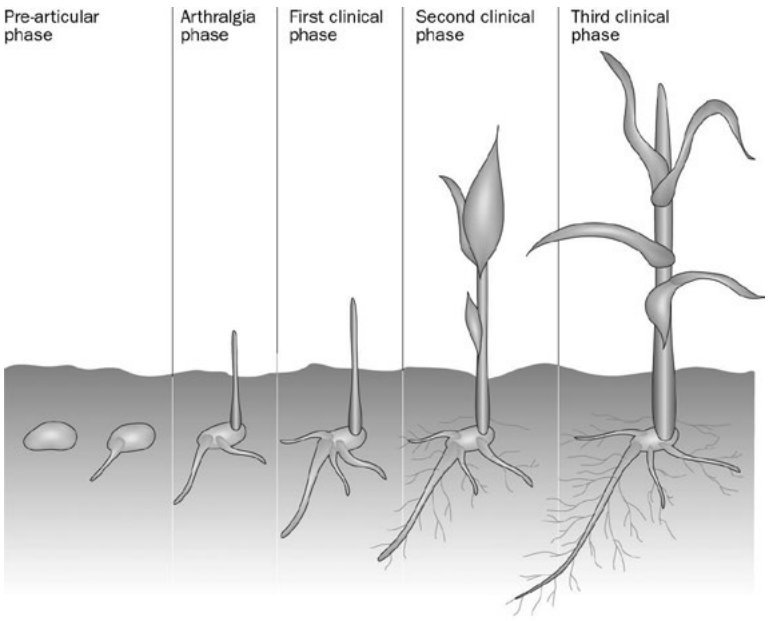

Figure 1. RA illustrated as stages of plant growth. With permission from Nature Reviews Rheumatology.

Treatment can be used to halt progression of RA. We know that early initiation of disease modifying antirheumatic drugs (DMARDs) is important [8,9,10,11,12]. A window of opportunity seems to exist in the first months since symptom onset [8,9,10]. If treatment is initiated in these 3 to 4 months, there will be significantly less joint damage, better work participation and a better quality of life [11,12]. This has led to a paradigm change to start treatment as early as possible, stressing the need for early diagnosis. As explained earlier, in the early phase when RA still lacks its defining features, it is difficult to distinguish those that have RA from those that have a transient form of arthritis [ref]. This leads to challenges both in primary and in secondary care [6,7,13,14,15].

Early recognition of RA in primary care

The incidence of inflammatory joint diseases such as RA in primary care is low [16]. The ROME study showed that yearly about 400 patients presented with new joint complaints of which only 6 were later diagnosed with an inflammatory joint disease in an average primary care practice in the Netherlands [17]. The low incidence of RA in primary care is most likely a fundamental problem in early recognition of RA. It probably leads to a lack of expertise on the part of the GP in recognizing synovitis [15]. As synovitis is a requirement in many referral guidelines it possibly causes referral delays.

To facilitate early referral of RA from primary care early arthritis clinics (EACs) have been established [6,18]. EACs provide GPs with a referral route for patients at risk for RA. Although this led to more timely referral as shown for the Leiden EAC, still delays of more than 4 months exist for at least 50% of RA patients [19]. Other initiatives at reducing delays include interventions such as combined consultations by GPs and rheumatologists and educational programs [18]. Formal testing of these interventions on delay are absent [18]. Given the importance to treat within 12 weeks of symptom onset, reducing delay further is important.

Early recognition of RA in secondary care

The challenges in secondary care are different from those in primary care. Patients can present with artralgia or synovitis [5,6,7,20]. If at physical examination synovitis is confirmed, the patient will undergo a number of diagnostic tests to confirm the presence of RA or another classifiable inflammatory disease. If no classifiable disease can be determined RA might still be the underlying disease explaining the synovitis. In this case the question is which patients will develop RA in the future. To predict RA development various prediction models exist including the 2010 ACR/EULAR criteria [21,22,23]. It is unknown which of these models has the highest diagnostic value in early disease.

The need for early identification of RA urged the development of new criteria to classify RA since the former set of criteria from 1987 was developed from a patient sample with established RA including features such as joint damage, nodules and a long disease duration, see table 1 [24]. The 2010 ACR/EULAR criteria were developed using prediction model methodology [24,25,26]. They showed promising results in the derivation cohort, but validation of the 2010 ACR/EULAR criteria was still necessary when they were presented in 2010.

Table 1. Classification criteria for rheumatoid arthritis from 1987 and 2010.

1987 classification criteria*	Score	2010 classification criteria**	Score
Morning stiffness > 60 minutes	1	1 large joint	0
Arthritis of 3 or more joints	1	2-10 large joints	1
Arthritis of hand joints	1	1-3 small joints	2
Symmetric arthritis	1	4-10 small joints	3
Rheumatoid nodules	1	> 10 joints (at least one small joint)	5
Rheumatoid factor positivity	1	Negative RF and anti-CCP	0
Radiographic changes typical for RA including erosions or decalcification	1	Low positive RF or low positive anti-CCP	2
		High positive RF or high positive anti-CCP	3
		Normal CRP and normal ESR	0
		Abnormal CRP or abnormal ESR	1
		Duration < 6 weeks	0
		Duration ≥ 6 weeks	1

* Items 1-4 must have been present for at least 6 weeks. Four of 7 items need to be present to classify as RA. ** The target population for these classification criteria are patients who have at least one joint with definite synovitis with the synovitis not better explained by another disease.

The other challenge in secondary care emerges if at physical examination synovitis cannot be confirmed but RA might still be the explanation for the symptoms. Some patients may be in an early phase of RA in which they only present with arthralgia. In this case, it is essential to recognize those patients that will develop inflammatory arthritis (IA) and perhaps RA in time. These patients can be either ACPA and/or RF positive or negative. Among patients that are ACPA and/or RF positive previous studies showed that about 20% of patients present with synovitis in 1 to 4 years [27,28]. In these patients risk factors for the development of IA were studied, but about a quarter to half of RA patients are ACPA and/or RF negative [19,29]. Information on the latter subsample is lacking including data on the development of synovitis and on determinants associated with development of synovitis.

The Rotterdam Early Arthritis CoHort

To address early recognition of RA – and preferably IA –the Rotterdam Early Arthritis CoHort (REACH) was set up in 2004 [30]. Patients eligible for REACH comprised of those that had IA according to the GP and those that had 2 painful joints and at least 2 predefined inflammatory characteristics, see box 1. These criteria were developed by the rheumatologists and PCPs that set up the REACH, based on tacit knowledge of inflammatory joint symptoms. Using these criteria resulted in a cohort that included a wide variety of inflammatory arthritis patients, both those with classified diagnoses and those with unclassified diagnoses. In addition it allowed for the inclusion of patients that presented with mere arthralgia. The population included in REACH allowed research into aspects of early recognition in different phases of RA.

Box 1. Eligibility criteria for patient inclusion in the Rotterdam Early Arthritis CoHort

At least one swollen joint OR **at least two joints tender or with restricted joint movement, plus two or more of the following criteria:**
1. Morning stiffness > one hour
2. Unable to make a fist in the morning
3. Pain when shaking someone's hand
4. Pins and needles in the fingers
5. Difficulty wearing rings
6. Difficulty wearing shoes
7. Family history of rheumatoid arthritis
8. Unexplained fatigue existing for less than one year

Aim and outline of this thesis

To address the main research aims this thesis was divided in two parts. Part one focuses on early recognition in primary care (chapter 2 and 3). The main aim here was:

- to assess delays in referral in REACH and to improve these delays.

In part two chapters 4 to 8 focus on early recognition of patients at risk for RA in specialized care. Here, two main aims were formulated.:

- to establish the occurrence of IA in arthralgia and to identify risk factors for patients that develop IA.
- to evaluate different diagnostic tests to diagnose RA early among patients with IA, including the diagnostic performance of the 2010 ACR/EULAR criteria.

Part one

In chapter 2 referral delays in REACH were evaluated as well as determinants associated with shorter delays. One of the determinants evaluated was whether recognition of synovitis by the GP was associated with shorter delays. Based on the findings from chapter 2 a referral tool was constructed to improve recognition of patients with synovitis at risk for IA and more in particular RA (chapter 3).

Part two

In chapter 4 the incidence of IA was determined in those patients included in REACH with mere arthralgia, without synovitis. Also various determinants were tested for their potential association with the development of IA. In chapter 5 an existing tool to identify patients that will develop IA over time among serology positive artralgia patients derived in Amsterdam was validated. In chapter 6 the diagnostic value of Dual Energy X-ray Absorptiometry (DEXA) measurements of the hand was tested for use in early IA. In chapter 7 the 2010 ACR/EULAR criteria for the early identification of RA were tested for diagnostic purposes and compared to existing prediction models for the development of

RA. Finally in chapter 8 the effect on diagnostic value of the 2010 ACR/EULAR criteria was evaluated when a different cut-off value was used.

Chapter 9 summarizes and discusses the results presented in this thesis.

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CHAPTER Two

Delay in referral of early arthritis.
Results from the Rotterdam Early Arthritis CoHort (REACH)

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Abstract

Introduction

Delayed treatment initiation in rheumatoid arthritis (RA) worsens prognosis. We set out to evaluate (i) delay in an early arthritis cohort (REACH) in 3 diagnostic groups: RA, other inflammatory arthritis (IA) , and inflammatory complaints without synovitis and, (ii) determinants associated with referral within 12 weeks, including the assessment of synovitis by the primary care physician (PCP).

Methods

We used data from the Rotterdam Early Arthritis/Arthralgia CoHort (REACH; n=434). Delay was analyzed using simple descriptive techniques for patient delay and PCP delay. To explore the association of the predefined determinants with timely referral univariate logistic regression was performed.

Results

Overall median delay was 13 weeks (IQR 1-52). In RA (n=80) median delay was 12 weeks (IQR 3-48), other IA(n=103) was seen within median 7 weeks (IQR 1-46) and inflammatory joint complaints without synovitis(n=218) was evaluated within median 16 weeks (IQR 2-52). Fifty-one percent of RA patients were seen within 12 weeks. This short delay was related to a positive CRP (OR 5.63, 95% CI 1.90-16.65). Recognition of synovitis by the PCP was not associated with short delay.

Conclusion

Despite the introduction of an early arthritis clinic, almost half of the RA patients were not seen within 12 weeks of symptom onset. Identification of synovitis by the PCP was not associated with timely referral indicating early referral strategies may require use of other determinants than requiring PCPs to recognize synovitis.

Introduction

Delayed treatment initiation in rheumatoid arthritis (RA) leads to an increased risk of structural joint damage and a lower chance of DMARD-free sustained remission [1,2]. Treatment within the first 12 weeks of symptom onset, the so called window of opportunity, prevents joint damage and disability, allowing people to stay at work and to maintain their quality of life [3,4,5]. Therefore timely referral from the primary care physician (PCP) to specialized care is critical. In order to shorten delays in referral early arthritis clinics (EACs) have been established [6,7]. Van der Horst-Bruinsma et al showed already in 1998 positive results on shortening delay by the introduction of the EAC in Leiden [8]. In 2010, van der Linden et al showed that referral within 12 weeks of symptom onset was associated with less structural joint damage. In this study swift referral of early IA patients regardless of diagnosis was associated with younger age, male gender, involvement of large joints, acute symptom onset, a higher C-reactive protein (CRP) and the absence of autoantibodies [2]. These determinants may represent a rapid disease onset, a feature previously described to be associated with swift referral [2,8], as well as other diagnoses such as gout.

Referral delay can be separated into two components: patient delay and PCP delay [9]. *Patient delay* occurs if a patient waits to see the PCP when symptoms first occur. It is influenced by the time needed for appraisal of the symptoms to be an illness, appraisal of the illness requiring medical care, willingness to getting medical care and scheduling delay [10]. This process is influenced by the patients surroundings - such as comments made by family-members - that either encourage or discourage patients to seek help for their complaints [11,12]. *PCP-delay* occurs when patients present with their symptoms to a PCP but referral to specialized care is delayed. The insidious onset of RA itself or the difficulty in recognizing synovitis has often been linked to PCP-delay as it prohibits easy identification of the onset of RA among more benign and usually self-limiting reasons for musculoskeletal complaints [6,11,13,14]. Therefore, in the first phase of RA, it is common practice to use a wait and see policy, which might add to referral delays [15].

To reduce delay one could raise awareness among PCPs, patients or both. Patients could be informed via public campaigns raising awareness on the risk of chronic inflammatory joint disease. Few studies tried this but the effect on patient delay was not evaluated to our knowledge [7]. Increasing awareness among PCPs might be a better way to reduce delays. This can be done for example by the implementation of EACs enabling early referral, circumvening waiting lists in secondary care [6]. The effect on delay has only been described for the Leiden EAC which had improved to 14 weeks for all EAC patients by 2010 compared to a delay of 37 weeks when the EAC was initiated [2,7]. Although many other EACs aim to reduce delay, no other data describing the effect in comparison to routine care is known to us [7]. In the Netherlands, in Leiden and Groningen, rheumatologists screen patients on the presence of synovitis in an Early Arthritis *Recognition* Clinic (EARC), an effort to further reduce delays in referral [1]. Our own cohort includes early arthritis as well as patients with recent inflammatory joint complaints [16]. All strategies aim to see patients with short symptom duration to enable early treatment of those patients that require immunomodulating therapy.

In the current study we set out to evaluate aspects of delay in the REACH. We did so by evaluating delays for 3 diagnostic groups: RA, inflammatory arthritis (IA) not RA, and patients with inflammatory complaints without synovitis. Furthermore, we evaluated determinants associated with referral within 12 weeks of symptom onset. These determinants included not only demographic and disease specific determinants, but also the assessment of synovitis by the PCP.

Materials and Methods

The Rotterdam Early Arthritis CoHort (REACH) is an ongoing, prospective, longitudinal cohort study set up in the greater Rotterdam area in July 2004. The REACH included patients referred by their PCP if they were older than16 years and had synovitis in one or more joint or pain in at least two joints for less than 12 months. At referral PCP's registered the reason for referral on a proforma. They could indicate the reason for referral: synovitis or joint complaints suspect for inflammation but without synovitis. For all patients referred by their PCP eligibility was checked in a structured telephone interview. Patients meeting the eligibility criteria were invited to attend the REACH clinic, where a trained nurse verified eligibility using the criteria listed in box 1. This criteria set was developed by the rheumatologists and PCPs that set up the REACH, based on tacit knowledge of inflammatory joint symptoms. Criteria such as difficulty wearing rings, making a fist in the morning and the presence of morning stiffness were formulated to grasp inflammatory characteristics. Eligibility was confirmed by a standard medical examination by a rheumatologist. Before taking part in the REACH cohort all study-participants gave informed consent, according to the guidelines provided by the Medical Ethical Committee of the Erasmus MC Rotterdam, the Netherlands.

REACH also included patients that were invited by their rheumatologists. These patients were not included in the current analysis, as we did not have information on referral reasons by the PCP.

Box 1. Eligibility criteria for patient inclusion in the Rotterdam Early Arthritis CoHort

At least one swollen joint OR at least two joints tender or with restricted joint movement, plus two or more of the following criteria:
1. Morning stiffness > one hour 2. Unable to make a fist in the morning 3. Pain when shaking someone's hand 4. Pins and needles in the fingers 5. Difficulty wearing rings 6. Difficulty wearing shoes 7. Family history of rheumatoid arthritis 8. Unexplained fatigue existing for less than one year

Data collection and determinants

A trained research nurse at the REACH clinic took a standardized history and physical examination, including blood and urine samples. Using a standard proforma data was collected about disease duration, first presentation at the PCP, articular symptoms, extra-articular symptoms, family history and previous medical history. Physical examination included measurement of blood pressure, height, weight, tender joint counts and swollen joint counts. Blood samples taken for routine diagnostic screening included IgM-RF (ELISA, Phadia), anti-CCP (Elia CCP on immunoCAP 250, Phadia), CRP (local standards) and ESR (local standards). X-rays of both hands and feet were assessed for the presence of bony erosions. Diagnoses were made by the consulting rheumatologist.

The following variables were considered as determinants to potentially influence timely referral; age, gender, acute or non acute onset of symptoms, red or warm joints observed by the patient, morning stiffness >60 minutes, VAS global complaints, tender and swollen joint counts, ESR, CRP, rheumatoid factor and anti-CCP. In addition the assessment of synovitis by the PCP was included in the analysis as a potential determinant of timely referral.

Definition of delay and window of opportunity

The window of opportunity was defined as symptom duration of less than 12 weeks in analogy to Nell et al, vd Linden et al and Nies et al [1,2,17]. To study different mechanisms contributing to delay we defined patient delay as the time between the onset of symptoms and the moment patients presented to their PCP. PCP delay was defined as the time between first presentation to the PCP and the first visit at the REACH clinic.

Statistical analysis

Simple descriptive techniques were used to describe delay. The Kruskal-Wallis test was used to test for differences between in delay between the three diagnostic groups. To explore the association of any of the predefined determinants with timely referral - within 12 weeks - univariate logistic regression was done stratified for the three diagnostic groups (RA, IA not RA and inflammatory complaints without synovitis)

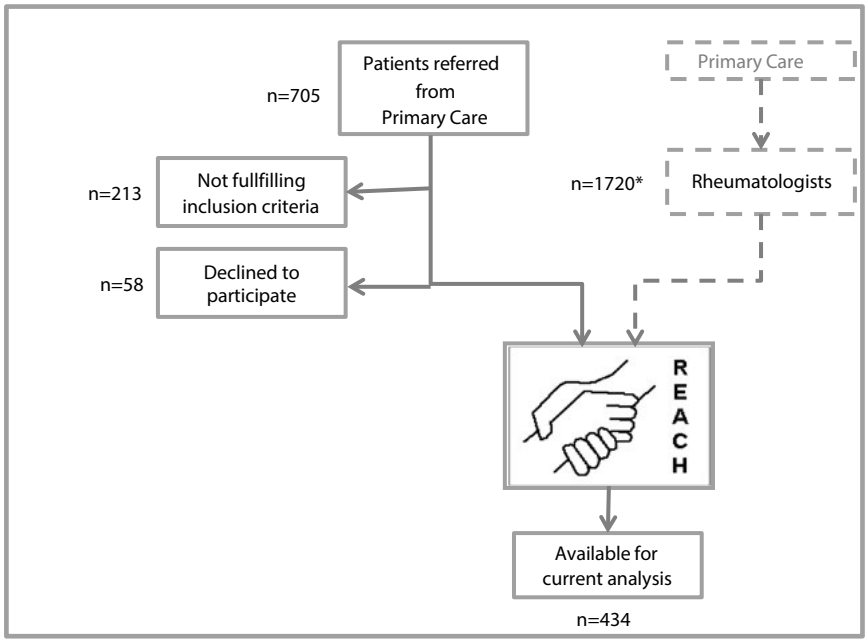
All analyses were carried out in STATA 13.0 SE.

Results

Until August 2011, 434 patients were referred directly by their PCP and included in REACH (see figure 1 for details on referral in REACH). Baseline characteristics of these patients are given in table 1. Of these patients, 83 patients (19%) were diagnosed with RA, either according to the 2010 ACR/EULAR classification criteria or the 1987 classification criteria (table 2) [18,19]. 112 patients (26%) had synovitis but were diagnosed with another inflammatory joint disease such as psoriatic arthritis or gout, or

were unclassified arthritis (UA), see table 2 for the diagnoses. In 228 (53%) of the patients referred by the PCP with inflammatory joint complaints no synovitis was found by the rheumatologist.

Figure 1. Inclusion of patients in REACH. Patients used for the current analysis were those referred by their PCP directly to REACH.



* Not included in the current analysis

Table 1. Baseline characteristics of patients included in REACH referred by their PCP.

Age, years (mean, SD)	49 (14)
Gender, female (n, percentage)	n=333 (77%)
Swollen joint count (median, IQR)	0 (0-23)
Tender joint count (median, IQR)	6 (0-33)
ESR (median, IQR)	12 (1-83)
C-reactive protein (median, IQR)	4 (1-99)
Rheumatoid Factor positive (n, percentage)	n=83 (19%)
Anti-CCP (n, percentage)	n=51 (12%)
Erosion (n, percentage)	n=7 (2%)
Family history positive for RA (n, percentage)	n=116 (27%)

Table 2. Diagnoses in REACH at baseline

Diagnosis	Number of patients (%)
RA, 2010 criteria or ACR 1987 criteria	83 (19%)
Unclassified arthritis	75 (17%)
Peripheral spondylarthropathies	10 (2%)
Systemic disorders*	9 (2%)
Cristal arthropathies	4 (1%)
Osteoarthritis with synovitis	43 (10%) 7 (2%)
Other diagnosis among patients with synovitis	7 (2%)
Patients with inflammatory complaints without synovitis	185 (43%)

* such as sarcoidosis, SLE and MCTD;* for n=11 patients (2%)the diagnosis is missing

Delay

The total delay in REACH was 13 weeks (IQR 1-52). Table 3 shows the referral delay in REACH as total delay, patient delay and PCP delay for the three diagnostic groups defined. For RA patients the delay was 12 weeks (IQR 3-48). The shortest median delay was for patients with IA not RA (7 weeks, IQR 1-46) and the longest median delay was for patient with inflammatory joint complaints but without synovitis at baseline (16 weeks, IQR 2-52). In RA patients patient delay accounted for 3 weeks (IQR 0-31) of the total delay, while PCP delay contributed 6 weeks (IQR 1-33). In those with IA not based on RA the highest median delay was again for PCP delay and not for patient delay (see table 3).

Fourty one of the RA patients (51%) were seen by the rheumatologist within 12 weeks of symptom onset, the window of opportunity in which optimal outcome can be expected from treatment (see table 3). Patients with IA not RA were more often referred within the window of opportunity than patients with RA (66% vs 51%) Patients with inflammatory joint complaints without synovitis were seen within 12 weeks of symptom onset in only 38%.

Table 3. Delays in REACH in weeks, stratified for the three diagnostic groups; RA, IA not RA and, inflammatory complaints without synovitis

	RA patients (n=80*)	IA not RA (n=103#)	Inflammatory complaints without synovitis (n=218^)	p-value$
Total delay in weeks (IQR??)	12 (3-48)	7 (1-46)	16 (2-52)	p<0.05
Patient delay	3 (0-31)	3 (0-27)	6 (0-45)	p<0.05
PCP delay	6 (1-33)	4 (0-35)	5 (0-50)	p<0.05
Total delay < 12 weeks	51%	66%	38%	p<0.05

* n=3 missings on delay for RA patients
# n=6 missings on delay for IA patients not RA
^ n=10 missings on delay for patients with inflammatory complaints without synovitis.
$ Kruskal-Wallis

Determinants associated with timely referral

In all REACH patients determinants indicative of more severe onset of symptoms were associated with timely referral: acute onset of symptoms (OR 4.58, 95% CI 2.89-7.25), red or warm joints (OR 1.55, 95% CI 1.05-2.29), swollen joint count (OR 1.06, 95% CI 1.00-1.13), ESR (OR 3.04, 95% CI 1.94-4.76) and CRP (OR 3.29, 95% CI 2.06-5.27). Among the subset of RA patients only CRP (OR 5.63 (95% CI 1.90-16.65) shows a significant association with timely referral (<12 weeks) For patients with IA not RA again CRP (OR 3.38, 95%CI 1.33-8.56) proved significantly associated with timely referral. Among the patients with IA not RA without synovitis a significant association was found with timely referral a positive ESR (OR 2.61; 95% CI 1.18-5.81), as well as for an acute onset of symptoms (OR 8.29; 95% CI 4.04-17.03).

Table 4. Univariate associations for timely referral to REACH (<12 weeks after symptom onset). Odds ratio's with corresponding 95% confidence intervals are shown

	RA patients (n=83) OR (95%CI)	IA not RA (n=109) OR (95%CI)	Patients with inflammatory complaints without synovitis (n=228) OR (95%CI)
Age, years	0.99 (0.96-1.02)	0.99 (0.96-1.01)	1.01 (0.99-1.04)
Gender, female	0.68 (0.23-2.00)	0.79 (0.34-1.84)	0.60 (0.29-1.24)
Acute onset of symptoms	2.61 (0.99-6.86)	2.05 (0.87-4.86)	8.29 (4.04-17.03)*
Red or warm joints as observed by the patient (present)	1.35 (0.56-3.24)	1.01 (0.44-2.28)	1.59 (0.90-2.82)
Morning stiffness > 60 minutes (present)	1.62 (0.66-3.98)	1.15 (0.49-2.72)	1.00 (0.54-1.87)
VAS, global complaints (continuous)	1.00 (0.98-1.02)	1.00 (0.98-1.02)	1.00 (0.99-1.01)
Swollen joint count (number)	1.03 (0.96-1.10)	0.96 (0.81-1.12)	n.a.
Tender joint count (number)	1.00 (0.94-1.06)	1.02 (0.93-1.11)	0.99 (0.95-1.03)
Rheumatoid factor positive	1.22 (0.51-2.93)	0.85 (0.19-3.77)	1.02 (0.44-2.36)
Anti-CCP positive	1.68 (0.69-4.09)	n.a.	1.02 (0.32-3.22)
ESR positive	2.26 (0.92-5.53)	2.32 (0.99-5.44)	2.61 (1.18-5.81)*
CRP positive	5.63 (1.90-16.65)*	3.38 (1.33-8.56)	1.78 (0.88-3.63)
Reason for referral, synovitis present according to PCP	0.73 (0.25-2.09)	2.37 (0.97-5.77)	1.62 (0.85-3.08)

*p<0.05

Discussion

In the current study we evaluated delay between symptom onset and referral to the Rotterdam Early Arthritis CoHort in three diagnostic groups. For RA patients we saw a median delay of 12 weeks. Patients with other inflammatory arthritis not RA had a median delay of 7 weeks, while patients with inflammatory complaints without synovitis had a delay of 16 weeks. We saw that 50% of RA patients were seen within 12 weeks - the window of opportunity -. Timely referral within 12 weeks of symptom

duration was associated with the typical features of acute onset and positive acute phase reactants. These associations were more pronounced in the other inflammatory arthritis patients than the RA patients. It is important to note that suspected synovitis by the PCP was not associated with timely referral (<12 weeks) in any of the diagnostic groups.

The REACH showed improvement in delays by providing PCPs with simple referral criteria and a swift referral route in the greater Rotterdam area in the current analysis. Our observed delay is similar to the delay in the recently initiated early arthritis *recognition* clinic (EARC) in Leiden and Groningen (the Netherlands). They observed 10 weeks delay in RA patients with 53% of patients seen within the window of opportunity [1]. In the EARC patients could be sent in for brief clinical evaluation by the rheumatologist if the PCP suspected synovitis without the necessity of synovitis upon physical examination [1]. Compared to historical data [20,21,22] both cohorts showed substantial reduction of delay. From this could be inferred that to reduce delay in clinical practice active intervention is needed by providing a quick referral route for patients with suspected IA, with or without preselection of patients using criteria indicative of inflammatory complaints in analogy to either the EARC or the REACH.

Despite improvements in both the EARC [1] and the REACH still half of the RA patients are referred with a disease duration longer than the window of opportunity which increases their risk of structural damage and functional disability [1,2,4]. Early referral was associated with acute onset suggesting that the more insidious onset of RA is not triggering awareness of the PCP to the disease. This may relate to difficulties in recognizing synovitis causing the PCP to apply a wait-and-see policy before referring the patient to the rheumatologist when symptoms persist. In order to further improve referral times in patients with RA or other forms of IA we need to define and test referral criteria that aid our PCPs to better identify patients with IA and thus better identifying those at risk for RA [13,14].

Limitations in our study include 1) the use of interview questions to ascertain the dates of first visit to the PCP and symptom start, 2) the absence of a precise date of actual referral by the PCP and the first visit at REACH and 3) the sample size. The first limitation to our data is the way we collected dates of symptom start and the first visit to the PCP. This was done by asking the patient when complaints started and when they first visited the PCP. Undoubtedly, these data are potentially subject to recall bias. Nonetheless, to study delays prior to referral, no other strategies are available. The second limitation with the definition of PCP delay is that we had no data on the specific date of referral, but we only had the first date of evaluation by the PCP for the current complaints. Thus we cannot formally demonstrate the length of our waiting list, but as a rule patients referred to the REACH clinic could be seen within a week. Finally, the evaluation of delay could be limited by our sample size, mainly as we stratified for diagnostic groups. It is not likely it influenced the point estimate of delay but it could have limited our chance of finding determinants associated with timely referral.

In conclusion, with a median delay of 12 weeks, about half of RA patients were seen outside the window of opportunity. This means that despite strategies to shorten delay, such as the EARC and our own EAC, there is still a need for improvement. As the identification of synovitis by the PCP was not associated with timely referral early referral strategies may need other features than requiring PCPs to recognize synovitis.

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CHAPTER

Three

Improving early referral of inflammatory arthritis

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Abstract

Introduction

Only a small proportion of patients with MusculoSkeletal Disease (MSkD) have inflammatory arthritis (IA). For them timely referral to a rheumatologist and early treatment could greatly improve their outcome. We aim to 1) assess the discriminatory ability of the general practitioner (GP) to correctly identify IA, 2) evaluate occurence of synovitis –in inflammatory (i)MSkD – 3) develop a referral tool

Methods

We drew on data from the Rotterdam Early Arthritis CoHort (REACH) using patients with suspected inflammatory joint complaints referred by their general practitioner GP. We tested sensitivity and specificity of recognition of IA by the GP compared to our evaluation. Using logistic regression we constructed the referral tool.

Results

Of 430 eligible REACH patients, 194 had IA confirmed by the rheumatologist. Reason of the GP for referral was available for 346 patients. 195 patients were referred without synovitis among which 77 (51%) patients had IA. Sensitivity of the GP to recognize IA was 0.49 (95% CI: 0.41-0.57) and specificity was 0.69 (95% CI: 0.62-0.75). The referral tool included history-taking items and MCP-MTP squeeze tests. It had a sensitivity of 0.81 (95% CI: 0.75-0.86) and a specificity of 0.57 (95% CI: 0.50-0.64) for identifying IA.

Conclusions

In REACH, 49% of IA patients would have been missed if our early referral procedure required the presence of synovitis. Our data suggest that early referral could be improved by providing a telephone service with a trained nurse or the use of a referral tool in primary care. Both need external validation.

Introduction

Early referral of inflammatory arthritis (IA) patients by general practitioners (GPs) has become important, as effective treatment exists to halt progression of persistent or erosive IA such as rheumatoid arthritis (RA) [1]. Recent studies showed that still 50% of RA patients are seen after 12 weeks of symptom duration despite introduction of Early Arthritis Cohorts (EACs) [Alves et al submitted,2]. In early stages of IA, patients present with symptoms similar to those in patients with more benign causes of musculoskeletal disease (MSkD): muscle soreness, stiffness, limited joint movement or painful joints [3,4]. GPs are confronted with the task of distinguishing the few patients with IA from the majority of patients with benign MSkD [3-6]. It is essential to identify the IA patients, in order to ensure that those at risk for persistent disease such as RA or PsA benefit fully from immunomodulating therapy [7-9].
As incidence of IA in primary care is low, GPs acquire little experience in detecting synovitis [3], which presumably accounts for the discrepancies in diagnosis found between rheumatologists and general practitioners in previous studies [4,10]. This limits the use of current early referral tools as most of them require the GP to detect synovitis [11-13]. GPs would benefit from an easy-to-use tool to guide referral of patients with IA without the need to detect synovitis [4].

In the Rotterdam Early Arthritis CoHort (REACH) set up in 2004[14,15], general practitioners could refer patients for early evaluation if they suspected IA or inflammatory MSkD (iMSkD) without the presence of synovitis. This information allowed us to 1) assess the discriminatory ability of the GP to correctly identify IA, 2) evaluate the occurence of synovitis –in the iMSkD – and finally 3) develop a referral tool for IA for use in primary care that does not require the detection of synovitis.

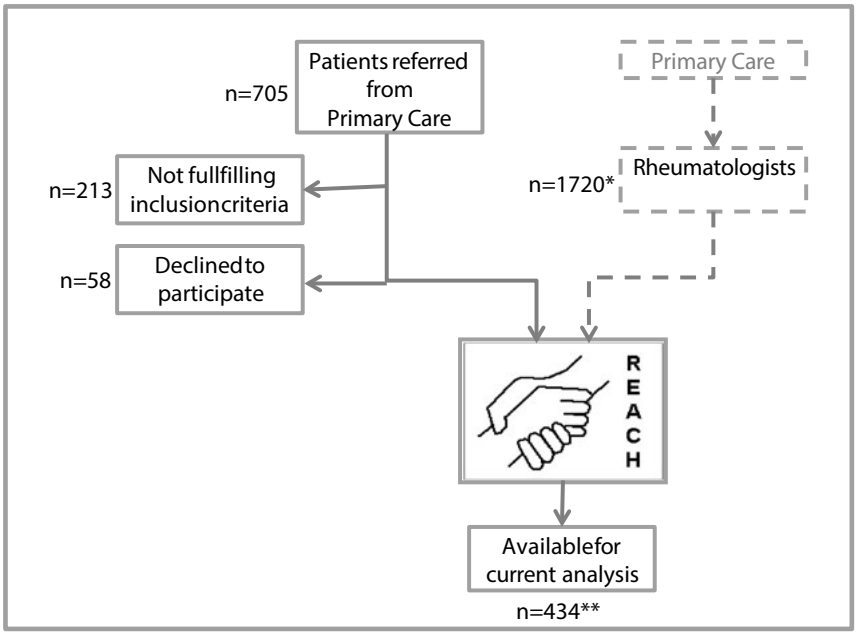
Patients and methods

Population

REACH is a prospective, inception cohort study set up in the greater Rotterdam area in July 2004. Patients were recruited via GPs or via rheumatologists from five outpatient rheumatology clinics at first consultation. For our analysis, we used only patients recruited via the GPs (see figure 1). Eligibility criteria for REACH were: older than16 years, joint complaints less than a year, with either synovitis in at least one joint or - in the absence of synovitis - pain in at least two joints in addition to two or more of the following criteria: morning stiffness for more than one hour; unable to clench a fist in the morning; pain when shaking someone's hand; pins and needles in the fingers; difficulties wearing rings or shoes; a family history of RA; or unexplained fatigue for less than 1 year. Eligibility was confirmed during a structured telephone interview using a standard proforma. Patients that met the eligibility criteria were invited to attend the REACH clinic, where a trained nurse verified eligibility using the criteria described previously. Eligibility was confirmed by a standard medical examination performed by a rheumatologist. Patients with symptoms related to trauma or overuse were excluded.

The study was approved by the local ethics committee and informed consent was obtainedfrom all participants.

Figure 1. Inclusion of patients in REACH.



*Not includedin the current analysis
** 4 patients had missing data on the outcomeand were therefor not included in the current analysis

Data collection

GPs filled out a standardized proforma where they could tick a box indicating if a patient was referred due to observed synovitis or whether it was due to joint complaints without synovitis (i.e. 2 painfull joints existing less than a year). During the subsequent telephone interview the items of our eligibility criteria were checked and painful, swollen and restricted joints reported by the patients were noted. At the first visit at the REACH clinic data was collected by our research nurses. This included taking a history using a standard proforma and a physical examination including a forty six joint count – the 44 joints of the DAS-44 and both temporomandibular joints. Also at the first visit blood was drawn to obtain the IgM rheumatoid factor (RF) (ELISA), anti-cyclic citrullinated peptide (anti-CCP) (EliA CCP on immunoCAP 250; Phadia Freiburg, Germany),CRP (local standards) and ESR (local standards).

Potential determinants

A broad array of potential determinants was considered for the association with synovitis. Three sources were used: self-reported complaints obtained during the telephone interview, data collected by the research nurse during the first visit and laboratory variables. Each laboratory value was cut off at the value provided by the manufacturer.

Case definition of inflammatory arthritis

A patient was identified as an IA case if physical examination at the first visit established the presence of synovitis in one or more joints. Synovitis was considered to be any soft tissue swelling, as assessed by our trained research nurses, and was confirmed by the attending rheumatologists. If the synovitis could be attributed to gout (confirmed by the presence of urate crystals), patients were not defined as cases (n=3).

Inflammatory MSkD was defined as no synovitis at physical examination and the presence of 2 or more painfull joints with 2 additional criteria, equal to our eligibility criteria.

Statistical Analysis

We used sensitivity and specificity to assess the discriminatory ability of the GPs to detect synovitis. To establish the occurence of IA we used simple descriptive techniques. To develop the referral tool we used statistical techniques from prediction methodology [16,17]. These techniques included a data reduction step, development of the referral tool, and an adjustment step to ensure easy applicability in practice as described below

Step 1 - data reduction

We considered a wide-range of variables as no clear-cut set of variables associated with IA was available from literature. Our sample size of 430 patients and an event rate of 194 IA cases allowed us to consider 19 candidate variables in a multivariate model [17]. To reduce the 83 available variables we clustered them in 1) signs and symptoms, 2) life style, 3) family history, 4) laboratory results, 5) extra-articulary complaints, 6) comorbidity, 7) time-related variables such as delay in presentation to the GP, and 8) medication (for details see the supplemental file). The number of variables in each cluster was reduced by stepwise backward logistic regression keeping only the variables that had a p-value<0.1 for the case definition previously described. Age and gender were kept as potential determinants of IA independent of statistical significance.

Step 2 - referral tool development

We fitted a logistic regression model with the variables identified in step 1 using a backward stepwise procedure (p-value<0.1) to create the referral tool without laboratory results. In two separate models we assessed whether adding acute phase reactants and RA-specific serology would be more discriminatory. A complete case analysis was done.

The tool's performance was tested using discrimination and calibration. For discrimination we calculated ROCs (receiver operating characteristics) curves and their corresponding AUCs (areas under the curve). For tool calibration we derived calibration plots [17]. To take account of optimism resulting from calculating performance in the same population used to develop our model, we drew 200 bootstrap samples from the dataset used to develop the model. [16-18]. This resampling method

is recommended for calculating adjusted performance measures in internal validation [15]. It results in an adjusted AUC and a shrinkage factor [16,18]. The shrinkage factor captures the overfitting of the internally validated model and should be applied to the model coefficients when using the referral tool on new data.

Step 3 - referral tool adjustment

To ease use in daily clinical practice, we translated the regression coefficients from the final models into weighted scores. To this end the regression coefficients of the variables were rounded to either .5 or .0 [15]. To evaluate whether the performance was affected, an AUC was calculated for the simplified models. In addition, sensitivity and specificity were calculated for each score, to obtain the cut-off value at which sensitivity and specificity are optimal for each model.

For all analyses, Stata 12.0 SE and R were used.

Results

430 out of 705 patients put forward as potential candidates by their GPs agreed to participate and were eligible for REACH (figure 1). Baseline characteristics for these patients are shown in table 1. Of the patients referred to REACH, 83 patients (19%) were diagnosed with RA, either according to the 2010 ACR/EULAR classification criteria (n=78) and/or the 1987 classification criteria(n=38), see table 1 [20,21]. Another 109 patients presented with synovitis but were diagnosed with another inflammatory joint disease such as psoriatic arthritis, gout, or had unclassified arthritis (UA).

Table 1. Patient characteristics

	Case (n=194)*	**Non-case (n=236)***	
Age, years (mean, sd)	50 (16) n=2 missing	47 (12) n=1 missing	p<0.05
Gender, female (n,%)	134 (69%)	199 (84%)	p<0.05
Duration of complaints, days (median, IQR)**	70 (7-366)	113 (9-365) n=1 missing	p< 0.05
Number of swollen joints (median, IQR)	2 (1-23)	0	p<0.05
Number of tender joints (median, IQR)	7 (0-33)	6 (0-32)	NS
ESR (median, IQR)	18 (2-67) n=2 missing	9 (1-49) n=4 missing	p<0.05
CRP (median, IQR)	6 (1-99) n=9 missing	3 (1-32) n=17 missing	p<0.05
Rheumatoid Factor (n, %)	53 (27%)	30 (13%) n=1 missing	p<0.05
Anti-CCP (n, %)	37 (19%)	14 (6%) n=1 missing	p<0.05
Erosion at baseline	7 (4%) n=4 missing	0 n=6 missing	p<0.05

Diagnoses	n=7 missing	n=7 missing	
Undifferentiated arthritis (n, %)	28 (18%)	0	p< 0.05
Osteoarthritis with or without synovitis (n, %)	20 (10%)	57 (24%)	p<0.05
Psoriatic arthritis (n, %)	6 (3%)	0	p<0.05
Diagnosis RA at baseline# (n, %)	49 (24%)	0	p<0.05

* Missing values n=4 # either according to 1987 classification criteria or a clinical diagnosis of RA

IA recognition among REACH patients

For 346 (80%) of the 430 patients a referral form from the GP was available. Missing forms were evenly distributed among cases and non-cases. Among these 346 patients 151 patients had IA and 195 patients had iMSkD according to the rheumatologist. Seventyfour (49%) of the 151 IA patients were referred by their GP suspected of IA. The other 77 IA patients were referred with iMSkD, see table 2. This resulted in a sensitivity to detect synovitis by the GP was 0.49 (95% CI: 0.41-0.57), indicating that 51% of the cases would be missed if a referral tool would require the presence of synovitis (see table 2). The specificity was 0.69 (95% CI: 0.62-0.75), indicating that in 31% of the patients the suspected synovitis by the GP could not be confirmed by the rheumatologist. This resulted in an AUC of 0.59.

Table 2. Discriminatory ability GP detection synovitis among the REACH patients (n=346*)

	Synovitis by the rheumatologist	**No synovitis by the rheumatologist**	
Synovitis by GP	74	61	135
No synovitis by GP	77	134	211
	151	195	346

* For n=84 (20%) no referral form was available

Referral tool development

Step 1: Data reduction

In the 8 clusters we identified 18 potentially relevant factors: squeeze test of metacarpophalangeal joints (MCPs) and metatarsophalangeal joints (MTPs), difficulty wearing shoes, difficulty wearing rings, self-reported restricted joint movement, self-reported painful joints, self-reported swollen joints, morning stiffness longer than 60 minutes, fatigue, self-reported fever, pins and needles, self-reported red or warm joints, self-reported low back pain, delay in presentation to the GP (in four categories), acute or chronic onset of symptoms, use of pain-relieving medication, ESR, CRP, and rheumatoid factor (RF).

Step 2: Development

Using the 18 variables from step 1 nine variables were retained in the multivariate model: gender, pain on squeezing the MCPs and MTPs, acute onset of symptoms, self-reported restricted joints,

self-reported painful joints, self-reported swollen joints, self-reported red or warm joints, delay in presentation, and the absence of fatigue (β coefficients for the association are presented in table 3). The mean AUC was 0.80 (95% CI 0.76-0.85) (table 3). The bootstrap-adjusted AUC was slightly lower: 0.77 (95% CI 0.72-0.82), see figure 2 for the corresponding ROC curve. Figure 2 also showes the calibration plots derived after bootstrap which shows a good calibration. On the basis of the AUC values, overfitting did not seem to be a major problem, though the shrinkage factor of 0.75 suggested some overfitting.

In addition to the referral tool described above, we also tested whether performance would be improved by adding the laboratory values for ESR and CRP (tool 2) or rheumatoid factor, ESR, and CRP (tool 3) (table 3). Adding acute phase reactants increased the AUC value to 0.82 (95% CI 0.78-0.87), whereas also adding RF resulted in an AUC of 0.84(95% CI 0.80-0.88). The bootstrap-corrected AUC values were slightly lower: see table 3. Calibration plots were still good for both tool's with the addition of laboratory values (figure 2).

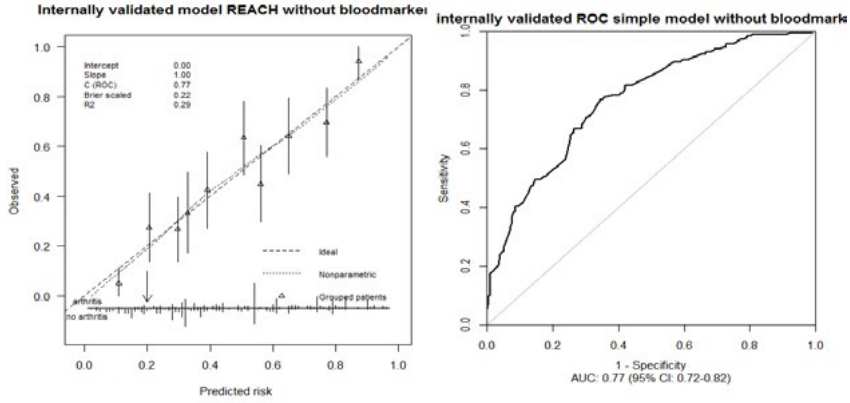
Table 3. Referral tools. The coefficients, weighted scores and performance measures

Variables	Tool 1: Basic tool		Tool 2: including ESR		Tool 3: including RF	
	β**	Score	β**	Score	β**	Score
Male gender	1.15	1	1.28	1.5	1.32	1.5
Positive squeeze test of MCPs and/or MTPs	0.90	1	0.82	1	0.91	1
Any loss of motion*	1.28	1.5	1.26	1.5	1.40	1.5
1 to 10 painful joints*	0.97	1	1.19	1	1.30	1.5
11 or more painful joints*	1.33	1.5	1.54	1.5	1.73	1.5
10 or more swollen joints*	1.92	2	1.97	2	1.94	2
Joints red and/or warm	0.89	1	0.81	1	0.74	0.5
Acute onset	0.30	0.5	-	-	-	-
No fatigue	0.69	0.5	0.64	0.5	0.58	0.5
Delay in presentation < 3 months, or > 6months	1.08	1	0.95	1	0.97	1
ESR (continuous)	-	-	0.05	ESR*0.05	0.05	ESR*0.05
CRP (continuous)	-	-	-	-	-	-
RF positive	-	-	-	-	0.90	1
Performance measures						
AUC (95% CI)	0.80 (0.76-0.85)		0.82 (0.78-0.87)		0.84 (0.80-0.88)	
Corrected AUC (95% CI)	0.77 (0.72-0.82)		0.81 (0.77-0.85)		0.82 (0.78-0.86)	
Shrinkage factor	0.75		0.74		0.74	

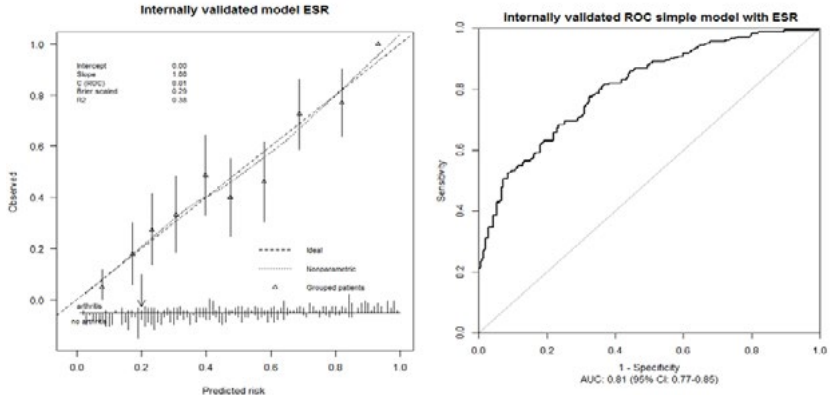
*Self-reported
** β = β coefficients

Figure 2. Calibration plots and ROC curves for the model without blood markers (2a), the model with ESR (2b) and the model with ESR and RF (2c)

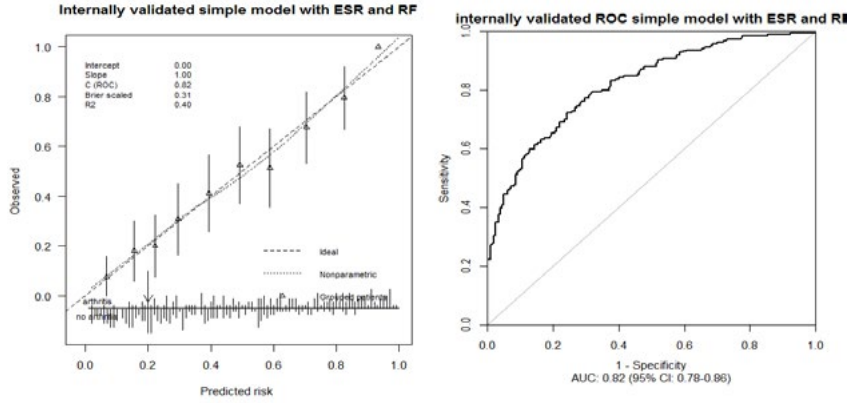
3.a.



3.b.



3.c.



Step 3: Adjusted referral tool

We transformed the results of the logistic regression model to a weighted score per variable (listed in table 3) running from 0.5 for acute onset and fatigue to 2.0 for more than 10 self-reported swollen joints. The resulting range was 0 –11, with higher scores indicating a greater probability of having IA. The AUC for the simple referral tool was 0.77 (95% CI 0.72-0.81), slightly lower than in the initial model. Table 4 shows, for each cut-off point in the score, the percentage true positive patients (sensitivity) diagnosed with IA and the percentage true negative patients (specificity) that did not have IA for each tool. The best balance for the basic tool — 81% true positive patients versus 57% true negative patients — was achieved at a score of 6 points. A score of 7 resulted in the best balance for the tool with the addition of ESR (sensitivity 0.73, 95% CI 0.66-0.80; specificity 0.69, 95% CI: 0.63-0.75) and also for the 3rd tool with added RF (sensitivity 0.82, 95% CI: 0.76-0.88; specificity 0.59, 95% CI: 0.52-0.66)

Table 4. Sensitivity and specificity at each potential cut-off for each referral tool.

	Tool 1: Basic tool		Tool 2: including ESR		Tool 3: including RF	
Cut-off	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
1	1.0	0	1.0	0	1.0	0
2	1.0	0	1.0	0	1.0	0
3	1.0 (0.98-1.0)	0.005 (0.00-0.03)	1.0	0	1.0	0
4	0.99 (0.97-1.0)	0.03 (0.01-0.07)	0.99 (0.97-1.0)	0.03 (0.01-0.06)	0.99 (0.97-1.0)	0.02 (0.01-0.05)
5	0.99(0.96-1.0)	0.19(0.14-0.25)	0.99 (0.96-1.0)	0.13 (0.09-0.19)	0.99 (0.96-1.0)	0.09 (0.05-0.13)
6	0.81(0.75-0.86)	0.57(0.50-0.64)	0.91 (0.86-0.95)	0.42 (0.35-0.49)	0.96 (0.91-0.98)	0.27 (0.21-0.33)
7	0.47 (0.40-0.55)	0.84 (0.79-0.89)	0.73 (0.66-0.80)	0.69 (0.63-0.75)	0.82 (0.76-0.88)	0.59 (0.52-0.66)
8	0.20 (0.15-0.27)	0.97 (0.93-0.99)	0.49 (0.41-0.57)	0.92 (0.88-0.95)	0.59 (0.51-0.66)	0.87 (0.82-0.91)
9	0.04 (0.02-0.08)	1.0 (0.98-1.0)	0.29 (0.22-0.36)	0.98 (0.95-1.0)	0.39 (0.32-0.47)	0.97 (0.94-0.99)
10	0	1.0	0.11 (0.07-0.16)	1.0 (0.98-1.0)	0.14 (0.09-0.20)	1.0 (0.98-1.0)
11	0	1.0	0.05 (0.02-0.09)	1.0 (0.98-1.0)	0.06 (0.03-0.11)	1.0 (0.98-1.0)
12	0	1.0	0.01 (0.001-0.04)	1.0 (0.98-1.0)	0.02 (0.01-0.06)	1.0 (0.98-1.0)
13	0	1.0	0.01 (0.001-0.03)	1.0 (0.98-1.0)	0.01 (0.001-0.03)	1.0 (0.98-1.0)
14	0	1.0	0.01 (0.001-0.03)	1.0 (0.98-1.0)	0.01 (0.001-0.03)	1.0 (0.98-1.0)

* IA was defined as any synovitis of one or more joints at physical examination at first visit

Discussion

Within REACH, an early arthritis referral cohort, 45% of patients had synovitis confirmed by the rheumatologist. Of these 51% were referred by the GPs with suspected inflammatory arthritis(IA), the other 49% were referred with iMSkD without synovitis identified by the GP. This resulted in a sensitivity of 0.49 and a specificity of 0.69 for the GP to identify synovitis. To ease recognition of IA by GPs we

developed a referral tool that does not require synovitis to be established by physical examination. It weights the following variables into a 0-11 score: gender, squeeze test, acute onset, duration between 3 - 6 months, absence of fatigue and the following self-reported joint problems: restricted movement, painful, swollen, red or warm. At 6 points the sensitivity was 0.81 (95% CI 0.75-0.86) and specificity was 0.57 (95% CI 0.50-0.64). Adding ESR would slightly decrease the sensitivity 0.69 (95% CI: 0.63-0.75) but would increase specificity to 0.73 (95% CI: 0.66-0.80).

To our knowledge this is the first data-driven referral tool for early IA [11]. Upto now referral recommendations were based either on expert opinion or on classification criteria for RA or PsA [1,11] and most of them required synovitis upon physical examination. The performance of our referral tool should be seen in the light of the choices we made. First, the referral tool was constructed in a selected population with a prior probability of 45%. Our selection criteria for REACH in itselve are already an improvement in referral of synovitis by the GP compared to the anecdotal evidence of 10-20% in usual secondary care. It would require a telephone service with a trained nurse who could apply the inflammatory criteria and asks for details on the affected joints. A patient that would have two painfull joints and two additional inflammatory criteria could then be further evaluate in clinical care. The referral tool we developed here could be applied directly in primary care. It would require either a paper version or a more easy web-based version that immediately provides a score to the family-doctor. With exception of the squeeze test the tool can be completed by the patients themselves. Both referal methods need further external validation as often data-driven tools perform better in the cohort they were derived from. Second, due to the data-driven approach some typical inflammatory features disappeared from the model such as morning stiffness. Although we found a significant relationship for morning stiffness in the univariate analysis, in the multivariate analysis it disappeared in favor of a positive squeeze test. In the laboratory extension models anti-CCP dropped out in the data-reduction phase because of its correlation with RF. Third, we chose a high sensitivity over specificity as we would like to apply the tool in primary care and preferred therefore the simple model without laboratory values. In settings where caseload in secondary care would be a problem one could consider the tool with ESR. It improves specificity at the costs of sensitivity. Fourth, we aim to identify all synovitis patients not differentiating between diagnoses in the stage of referral. This means that after referral to rheumatology practices the risk of RA can be further ascertained in these patients by applying the 2010 criteria or the specialists' expertise [20].

In conclusion, in REACH, 49% of the IA patients would have been missed our early referral procedure would have required the presence of synovitis. Our data suggest that early referral could be improved by providing a telephone service with a trained nurse or the use of a referral tool in primary care. Both need external validation.

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CHAPTER

Four

The incidence and risk factors of inflammatory arthritis in arthralgia

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Abstract

Objective

Identifying patients at risk for IA in the arthralgia phase may result in more timely treatment of patients with IA, in particular those with rheumatoid arthritis (RA). This study describes incidence of IA among patients with inflammatory arthralgia with symptoms < 12 months and explores characteristics potentially associated with IA occurrence.

Methods

We analysed data from 400 patients with arthralgia in 2 or more joints and inflammatory complaints but without synovitis from the Rotterdam Early Arthritis CoHort (REACH). The 1-year incidence of IA - *defined as soft tissue swelling at examination or DMARD treatment* - was determined. Characteristics associated were identified using univariate logistic regression.

Results

One-year incidence of IA was 15% (95% CI 11.5-18.5). This was strongly associated with the presence of ACPA (OR 6.31, 95% CI 3.07-13.00). Other factors associated in univariate analysis were a positive RF (OR 3.79, 95% CI 1.75-8.21) and a positive ESR (OR 4.12, 95% CI 2.21-7.67). Presence of small tender joints was negatively associated (OR 0.41, 95% CI 0.22-0.76). In the subset ACPA-RF negative patients the incidence was 12 % (95% CI 8.5-15.5). This was related to small tender joints (OR 0.37 95% CI 0.18-0.77) and ESR(OR 3.00 95%CI 1.40-6.40).

Conclusion

Fifteen percent of patients with arthralgia developed IA within one year. ACPA, RF and ESR were positively associated, while presence of small tender joints was associated with the absence of IA. Among the subsample of seronegative patients the incidence of IA was 12% with ESR and small tender joints positively associated.

Introduction

Patients presenting with mere arthralgia pose a diagnostic dilemma to rheumatologists. Arthralgia can be a precursor to inflammatory joint disease such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) or systemic lupus erytromatodes (SLE) [1,2,3]. While probably the majority of patients with arthralgia will have benign disease. Data from studies in RA suggest that detrimental effects such as joint destruction, reduced quality of life and increased mortality can be prevented by treatment in the earliest phases of the disease [4,5,6]. This evidence is also emerging for PsA [7,8]. The question arises whether patients could be identified even before the first synovitis is observed [9]. If identification in this presynovitis phase would be possible, perhaps research could establish how mere arthralgia progresses to inflammatory arthritis (IA) [3]. With better understanding, we may be able to target these processes to treat patients in this presynovitis phase preventing further evolution to chronic IA altogether [9,10].

Data on the incidence of IA in arthralgia patients and associated clinical characteristics is limited. Despite a fair amount of early arthritis cohorts [11], only four cohorts include patients with arthralgia [11,12,13,14]. Two cohorts studied arthralgia patients that were positive for IgM-RF (IgM rheumatoid factor), ACPA (anti-citrullinated protein antibody), or both [12,13]. Over a median of 11 months Bos et al observed 20% incident IA cases among 147 patients, while within 4 years a 27% incidence was described by de Hair et al among 55 patients [12,13]. Associations were found for ACPA, morning stiffness, smoking, alcohol use, BMI and dyslipidemia [12,13,15,16,17,18]. Up to now only one study reported on risk for IA in RF and ACPA negative arthralgia patients [19]. Over a median follow-up of nine months 8% IA was observed in 61 patients. More data is needed on the relevance of active surveillance in RF and ACPA negative arthralgia patients as a quarter to half of patients with persistent arthritis is RF and ACPA negative [20,21].

This study describes the one-year incidence of IA and in particular RA among patients with early arthralgia (i.e. less than 12 months) – *irrespective of ACPA or RF status*- in the Rotterdam Early Arthralgia/ Arthritis CoHort (REACH) and explores characteristics associated with incident IA.

Patients and methods

The REACH included patients both with and without synovitis at baseline with a symptom duration of less than 12 months [14, 22]. For the present analysis we used patients without synovitis with arthralgia from the REACH. If patients presented without synovitis, they had to have pain or loss of movement in at least two joints present for less than 12 months and fulfilled at least two of the additional eligibility criteria: morning stiffness for more than 1 hour; unable to clench a fist in the morning; pain when shaking someone's hand; pins and needles in the fingers; difficulty wearing rings or shoes; a family history of RA; or unexplained fatigue for less than 1 year. Patients with symptoms related to trauma or overuse were excluded. Eligibility was checked at the first visit to the REACH clinic and confirmed by a rheumatologist. All study-participants gave informed consent before taking part in the REACH

cohort, according to the guidelines provided by the Medical Ethical Committee of the Erasmus MC Rotterdam, the Netherlands.

Data collection

At the first visit a trained research nurse at the REACH clinic took a standardized history and physical examination, including blood and urine samples. Using a standard proforma data were collected on articular symptoms, extra-articular symptoms, family history and previous medical history. Physical examination included measurement of blood pressure, height, weight, tender joint scores, swollen joint scores, and impaired movement for each joint [see supplement 1]. Blood samples were taken for routine diagnostic screening, including IgM-RF (ELISA), anti-CCP (EliA CCP on immunoCAP 250, Phadia) and ESR (Westergren method). Clinical diagnoses were made by the consultant rheumatologist. After 6 and 12 months patients were reassessed by our research nurses including a physical examination and blood samples.

Case definition

An IA case was defined as a patient with observed synovitis by the rheumatologist over the course of one year after the first consultation [see supplement 1 for the evaluated joints]. For all IA cases we checked the diagnosis at 12 months including fulfilment of the 2010 ACR/EULAR criteria as well as the ACR 1987 criteria [23,24].

Potential characteristics

After consideration of the available literature [13, 17, 24, 25, 26, 27, 28, 29] the following variables were identified as characteristics that are potentially associated with development of IA.

Personal characteristics

We considered age, gender, alcohol use, smoking and BMI [17, 25, 26, 27]. Alcohol use was defined as more than 1 consumption of alcohol a day. Smoking was defined as current smoking or smoking cessation in the last 15 years in analogy to di Giusepe et al [28]. We defined overweight as a BMI ≥ 25 to allow comparison to the data from de Hair et al [13].

Clinical characteristics

From the physical examination, we evaluated tender joint count (TJC), presence of small tender joints, presence of large tender joints, symmetry of tender joints, small tender joints with symmetric distribution, large tender joints with symmetric distribution [17, 27, 29]. Also, morning stiffness, family history of RA, use of pain medication, ESR, CRP, RF and ACPA were evaluated as potentially associated clinical characteristics [17, 24, 25, 26, 27, 29]. Wrist, PIP joints, MCP joints and MTP joints were regarded small joints while shoulders, elbows, hips, knees and ankles were defined as large joints following the

ACR/EULAR 2010 classification criteria for RA [24]. For morning stiffness a cut-off of 60 minutes was used. ACPA and rheumatoid factor were cut-off at the values provided by the manufacturers. This same rule was applied to ESR and CRP as binary covariates. For women, gender specific items such as previous pregnancies and hormone use were tested.

Statistical analysis

Simple descriptive techniques were used to describe the baseline factors and the 1-year incidence of IA. Univariate logistic regression was used to analyse the association between the potential characteristics and the presence of IA for all patients. BMI, ESR and CRP were tested continuously and dichotomously. The analysis was repeated stratified on ACPA and RF status. All analyses were carried out in STATA 12.0 SE.

Results

Four hundred patients with arthralgia without synovitis were included in REACH. Baseline characteristics are described in table 1. IA patients were on average 45 years old and they were predominantly female. Fifty nine patients (15%, 95% CI 11.5-18.5) were identified as a case of incident IA within one year of which 40 (of 344) patients were negative on ACPA and RF and 19 (of 54) patients were either ACPA or RF positive. Incident cases had slightly higher levels of ESR and CRP. For 2 patients data on ACPA was missing.

Table 1. Baseline characteristics for n=400 patients with arthralgia

Age (years), mean (sd)	46 (13)
Gender (female) n (%)	333 (83%)
Duration of complaints (days), median (IQR)	131 (71-203)
TJC (number), median (IQR)	6 (2-11)
RF* positive, n (%)	33 (8%)
ACPA* positive, n (%)	37 (9%)
ESR (mm/hour, median (IQR)	10 (5-18)
CRP (mg/l), median (IQR)	3 (1-8)

* all samples for RF and ACPA were analysed at the Erasmus MC, Rotterdam, the Netherlands

Incidence of IA, RA and other diagnosis

Of the 59 incident IA cases 21 (36%) patients fulfilled either the 2010 revised criteria or the1987 criteria, 7 of these 21 only fulfilling the 1987 criteria. ACPA and/or RF was found in 13 out of the 21 RA patients. Besides classifiable RA, diagnoses among the other 38 patients were RA according to the physician (n=9), unclassified arthritis(n=23), inflammatory arthritis due to osteoarthritis (n=5) and one case of mixed connective tissue disease. For 2 patients information on diagnosis was missing.

Characteristics associated with the incidence of inflammatory arthritis

No significant assocations were found between personal characteristics and IA in the univariate analyses. The clinical characteristics univariately associated with IA were presence of small tender joints (OR 0.41: 95% CI 0.22-0.76), a positive ESR (OR 4.12: 95% CI; 2.21-7.67), a positive RF (OR 3.79: 95% CI; 1.75-8.21) and ACPA (OR 6.31: 95% CI; 3.07-13.00), see table 2. An unexpected finding was the odds ratio for presence of small tender joints.

In the subsample of ACPA and RF negative patients (n=344) a positive ESR (OR 3.00: 95% CI 1.40-6.40), morning stiffness longer than 60 minutes (OR: 2.04: 95% CI 1.04-4.00) were associated with development of IA within a year. Again small tender joints proved a protective characteristic (OR 0.37, 95% CI; 0.18-0.77).

In the ACPA and/or RF positive patients (n=54) subsample IA was associated with duration of complaints and ESR A longer duration of complaints was protectiveOR 0.99 (95% CI; 0.98-0.99). A positive ESR showed an OR of 8.17 (95% CI; 2.13-31.42). None of the other variables showed an association with the development of IA within a year.

Table 2. The strength of the association of each of the tested characteristics with the incidence of IA based on univariate.

	All patients (n=400)	Seronegative patients (n=344)	Seropositive patients (n=54)
Personal Characteristics			
Age (years)	1.02 (0.99-1.04)	1.01 (0.98-1.03)	1.04 (0.99-1.10)
Gender (female)	0.61 (0.31-1.19)	0.84 (0.35-2.02)	0.51 (0.15-1.72)
Alcohol more than 1 consumption	0.53 (0.12-2.33)	0.40 (0.05-3.07)	#
Smoking current or in last 15 years	1.56 (0.88-2.76)	1.62 (0.82-3.20)	1.42 (0.44-4.52)
BMI (continuous)	1.02 (0.96-1.08)	1.02 (0.95-1.09)	1.04 (0.92-1.19)
>25	1.01 (0.54-1.89)	0.92 (0.44-1.95)	1.50 (0.43-5.27)
Clinical characteristics			
Tender joints			
Tender Joint Count (TJC)	1.00 (0.96-1.04)	1.00 (0.95-1.04)	(0.95-1.10)
Symmetry of tender joints (present)	0.99 (0.91-1.08)	0.99 (0.09-1.10)	1.05 (0.88-1.27)
Large tender joints (present)	1.08 (0.62-1.90)	1.31 (0.66-2.62)	1.07 (0.35-3.27)
Small tender joints (present)	0.41 (0.22-0.76)*	0.37 (0.18-0.77)*	0.75 (0.22-2.56)
Small tender joints with symmetric distribution (present)	0.77 (0.44-1.34)	0.52 (0.26-1.04)	3.0 (0.94-9.54)
Large tender joints with symmetric distribution (present)	1.53 (0.87-2.71)	1.73 (0.89-3.40)	1.84 (0.52-6.60)
Symptoms			
Morning stiffness >60 minutes	1.60 (0.90-2.85)	2.04 (1.04-4.00)*	0.98 (0.25-3.14)
Duration of complaints (days)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.98-0.99)*
VAS global (0-100mm)	1.00 (0.99-1.01)	1.00 (0.99-1.02)	1.01 (0.98-1.04)
Blood markers			

ESR (positive)	4.12 (2.21-7.67)*	3.00 (1.40-6.40)*	8.17 (2.13-31.42)*
CRP (positive)	1.31 (0.65-2.63)	1.56(0.70-3.50)	1.29 (0.25-6.60)
RF (positive)	3.79 (1.75-8.21)*	-	1.14 (0.36-3.61)
ACPA (positive)	6.31 (3.07-13.00)*	-	1.49 (0.35-6.41)
Obstetric history			
OAC / hormone use (present in females)	0.69 (0.14-3.30)	1.01 (0.12-8.36)	1.01 (0.12-8.36)
Number of pregnancies	0.64 (0.30-1.35)	0.58 (0.25-1.33)	0.63 (0.09-4.33)
Number of deliveries	1.21 (0.48-3.03)	1.12 (0.41-3.07)	0.88 (0.07-10.75)
Other			
Use of any pain medication	0.89 (0.46-1.72)	0.93 (0.42-2.08)	0.78 (0.21-2.94)
Family history RA (1st or 2nd degree relative)	1.52 (0.86-2.68)	1.29 (0.65-2.56)	2.13 (0.68-6.65)

*$p<0.05$
omitted as only one person drank any alcohol in all seropositive patients

Discussion

The one-year incidence of inflammatory arthritis (IA) was 15 % among REACH patients with early arthralgia (i.e. less than 12 months) with inflammatory characteristics. Twenty-one of these 59 patients (36%) were classified as RA according to the 2010 ACR/EULAR criteria or according to the 1987 ACR criteria. Incident IA was univariately associated with small tender joints, ESR, RF and ACPA. The association with small tender joints reduced the chance of IA. In the subsample of ACPA and RF negative arthralgia patients (n=344) 40 patients (12%) had incident IA. In these patients IA was univariately associated with ESR, small tender joints and morning stiffness, with small tender joints reducing the risk on IA. In the subsample of ACPA and RF positive patients (n=54) 19 cases were identified (35%). Association were observed for ESR and duration of complaints.

Comparing our results with previous studies we observe similarities but also differences [12,13]. Among the ACPA and/or RF positive patients we observed an higher incidence, but this may relate to our small sample size compared to the sample size of Bos et al [12] and de Hair et al [13]. In the ACPA and RF negative group we observed also a higher incidence compared to Steenbergen et al [19]. This could be related to our larger sample size and longer observation period and possibly the different selection criteria. When we investigated characteristics potentially associated with incident IA, we could confirm that ACPA was strongly associated in our population which was not selected based on RF or ACPA. Other factors previously described to increase the risk of IA are morning stiffness, smoking, BMI and dyslipidaedimia [13, 15, 16, 17]. In our present study morning stiffness was only associated with IA among the subsample of ACPA and RF negative patients. Smoking and BMI were not associated in our cohort, while Hair et al observed an association for BMI and smoking combined. When we looked at smokers with a high BMI we saw a small increase in IA frequency to 20% which is significantly lower than the 60% seen by the Hair et al [13]. Perhaps the association between smoking and BMI with the occurrence of IA mainly exists for patients that are ACPA positive [30]. In this our

small subsample though we could not demonstrate this association. Dyslipidemia was not analyzed as we did not have information on dyslipidimia.

In addition to characteristics that have been previously described, we also tested a variety of other clinical characteristics. Most of these tested variables did not show an association to the presence of IA after 1 year. ESR and presence of small tender joints did however. ESR positivity was associated with IA. To our knowledge ESR has not been tested previously although CRP has. CRP did not show any association with developing arthritis in the previous studies [17, 31], which was also the case in our study. The presence of small tender joints seems to reduce the risk of IA This is counterintuitive as small joints are frequently affected in RA patients. Within our sample many patients (81%) had tender joints of their hands and feet which might cause a change in the relation between those that developed IA and those that did not.

Our study has strengths and limitations. The strength of our study lies in its patient selection and availability of a wide range of personal and clinical characteristics. The patient selection allowed us to investigate arthralgia patients independent of auto-antibody serology. This enabled us to study the subsample of seronegative patients in addition to seropositive patients. A limitation of our study is the possibility that primary care physicians selected their patients on unmeasured factors in addition to the selection criteria that were offered for the referral of patients to REACH. For instance, we saw that our typical patient was middle-aged and female. This is the typical population at risk for RA, but we may have an underrepresentation of patients that were younger and/or male. This might have affected our results; however we cannot be certain to what extent. Another limitation is that due to the limited amount of events we decided to do an exploratory analysis using univariate analysis without a multivariate analyses. The relevant contribution of each of the observed associations requires further investigation in a larger sample.

In this study we followed patients with arthralgia for one year; the incidence of IA was 15%. IA was associated with small tender joints, morning stiffness, ESR and ACPA in the univariate analysis. Among the subsample of seronegative patients the incidence of IA was 12%. Only ESR and small tender joints were associated with this development. These results brings us a little bit closer to target patients in this presynovitis phase but other biomarkers maybe necessary to increase the number of patients identified at risk for IA.

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CHAPTER Five

External validation of a prediction rule for development of inflammatory arthritis in autoantibody-positive individuals

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Abstract

Background

Autoantibodies can be present years before clinical signs of rheumatoid arthritis (RA). A recently presented prediction model for the development of inflammatory arthritis (IA) in autoantibody-positive individuals was validated here.

Methods

The validation cohort consisted of individuals from the pre-arthritis cohort of the Academic Medical Center (AMC) in Amsterdam and the Rotterdam Early Arthritis Cohort (REACH) who were positive for IgM rheumatoid factor and/or anti-citrullinated protein antibodies, without synovitis. Performance was tested using receiver operating characteristic (ROC) curves including an area under the curve (AUC) and calibration plots for development of IA within 1 and 2 years. Diagnostic performance after 2 years was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratio's (LR) for different cut-offs.

Results

The validation cohort consisted of 154 individuals, of whom 32 (21%) developed IA within one year and 47 (31%) within 2 years.

The AUC of the ROC curve at 1 and 2 years were 0.74 (95% CI: 0. 72-0.76) and 0.73 (95% CI: 0.75-0.75). Calibration plots were reasonable. Sensitivity and specificity were optimal at a score of 7 with a sensitivity of 0.65 (95% CI: 0.51-0.79) and specificity of 0.71 (95% CI: 0.61-0.80), PPV of 0.50 (95% CI: 0.37-0.63), NPV of 0.82 (95% CI: 0.74-0.90), LR+ of 2.2 (95% CI: 2.07-2.43) and LR- of 0.49 (95% CI: 0.45-0.54).

Conclusion

Discrimination and calibration of the model to predict development of IA were reasonable. When evaluating diagnostic performance sensitivity and specificity were optimal at a score of 7.

Introduction

Research in the field of rheumatoid arthritis (RA) is gradually shifting towards the earlier phases of the disease as the ultimate goal would be to prevent rather than to treat RA [1] . Several risk factors for the development of RA have been determined, such as genetics and environmental factors. Each set of risk factors is thought to represent a phase in the development of RA [2]. We have previously observed that smoking and overweight increase the risk of developing arthritis in individuals having systemic autoimmunity associated with RA [3]. Many years before onset of RA the RA-specific autoantibodies IgM rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA) can be present indicating an immune response although the disease is not yet clinically apparent [3–6]. Targeting this immune response seems plausible as months to years before the onset of clinically apparent arthritis clear synovial inflammation is absent [6].

If research is to continue towards preventive treatment regimens it is important to be able to accurately predict who will develop RA and who will not. Recently, in a large cohort of individuals positive for IgM-RF and/or ACPA but without signs of clinically apparent synovitis a prediction rule was developed to predict the progression to inflammatory arthritis (IA) [7]. This prediction rule includes the levels of autoantibodies as well as of easily applicable questions about joint symptoms, alcohol use and a family history of RA, which would make it a feasible tool to use in rheumatology practices. Validation of the prediction rule for the development of IA in individuals positive for IgM-RF and/or ACPA but without synovitis should occur in an independent cohort. Cohorts including such patients are few though. To our knowledge, the largest existing cohorts at the moment with available information on the development of IA and appropriate follow-up, other than the development cohort, are the pre-arthritis cohort of the Academic Medical Center (AMC) in Amsterdam and the Rotterdam Early Arthritis Cohort (REACH), Rotterdam, the Netherlands. In the current study we aimed to externally validate this prediction rule using patients from both cohorts to evaluate whether the model is generalizable to autoantibody-positive individuals outside the development cohort.

Methods

Validation cohort

To establish a validation cohort we included individuals who were positive for RF and/or ACPA, without any evidence of synovitis upon physical examination. These patients were participating in the pre-arthritis cohort of the AMC or in REACH.

In the AMC cohort individuals had arthralgia and/or a positive family history for RA and were included between June 2005 and January 2013. IgM-RF was measured using IgM-RF ELISA (Sanquin, Amsterdam, the Netherlands (upper limit of normal (ULN) 12.5 IU/mL)) until December 2009 and thereafter using IgM-RF ELISA (Hycor Biomedical, Indianapolis, IN (ULN 49 IU/mL)). ACPA was measured using anti-CCP2 ELISA CCPlus (Eurodiagnostica, Nijmegen, the Netherlands (ULN 25 kAU/L)). In this

cohort individuals were recruited via the outpatient clinics of the department of Clinical Immunology and Rheumatology of the AMC or via testing family members of RA patients seen at the outpatient clinics or at public fairs across the Netherlands for the presence of IgM-RF or ACPA.

In the REACH cohort study subjects had joint symptoms for a maximum period of 12 months, consisting of two or more joints with pain or loss of movement and ≥2 of the following criteria: morning stiffness >1 hour, unable to clench a fist in the morning, pain when shaking someone's hand, pins and needles in their fingers, difficulties wearing rings or shoes, a family history of RA, or unexplained fatigue < 1 year. Individuals were included between November 2004 and April 2009. IgM-RF was measured using IgM-RF ELISA (Phadia, Freiburg, Germany; ULN 12 IU/mL) and ACPA using ELIA CCP on immunoCAP 250 (Phadia, Freiburg, Germany; ULN 10 IU/mL). These individuals were recruited via general practitioners and several outpatient rheumatology clinics in the greater Rotterdam area. The study was performed according to the principles of the Declaration of Helsinki. The cohorts were approved by their institutional review boards of the AMC or the Erasmus Medical Center (EMC), and all study subjects gave written informed consent.

Variables included in the prediction rule

The prediction rule consists of 8 binary items and 1 categorical item: having a first degree relative (FDR) with RA; no use of alcohol; start of symptoms less than 12 months ago; intermittent symptoms; having symptoms in both upper and lower extremities; visual analogue scale (VAS) pain of at least 50; morning stiffness of at least 1 hour; patient notification of joint swelling and autoantibody status, see box 1. The binary items are assigned a value of 1 if present, except for the VAS pain for which 2 points are obtained. The autoantibody status item combines IgM-RF- and anti-CCP-status into 4 categories: IgM-RF positive (pos) and anti-CCP negative (neg), 0 points; IgM-RF neg and anti-CCP pos < 3x ULN, 2 points; IgM-RF neg and anti-CCP pos ≥ 3x ULN, 3 points; IgM-RF and anti-CCP pos, 4 points [7].

For both validation cohorts extensive clinical history was taken at inclusion. However, not all items from the original prediction rule were collected in a similar way. In the AMC cohort the items concerning joint symptoms (items 3, 4, 5, and 8) were not explicitly asked for. These items were retrospectively obtained from the medical charts. In the REACH cohort items 1 and 6 were defined differently. Family history included also second degree relatives in REACH, while joint pain was assessed using a Likert scale of 0-10 instead of a VAS. A score of at least 5 was considered comparable to a VAS score of at least 50. As one of the inclusion criteria in REACH was duration of complaints less than a year, item 3 was positive by definition for REACH patients. In case of missing values of any item medical charts were reviewed for both cohorts. When no clear description of an item was available, an item was scored as missing.

Box 1. The 9 items of the prediction model [7].

1. having a first degree relative with RA, 1 point if present
2. no use of alcohol, 1 point if present
3. start of symptoms less than 12 months ago, 1 point if present
4. intermittent symptoms, 1 point if present
5. having symptoms in both upper and lower extremities, 1 point if present
6. VAS pain of at least 50, 2 point if present
7. morning stiffness of at least 1 hour, 1 point if present
8. patient notification of joint swelling, 1 point if present
9. IgM-RF- and anti-CCP-status in 4 categories:
   - IgM-RF positive and anti-CCP negative, 0 points
   - IgM-RF negative and anti-CCP positive < 3x cut-off, 2 points
   - IgM-RF negative and anti-CCP positive ≥ 3x cut-off, 3 points
   - IgM-RF and anti-CCP positive, 4 points

Time to IA and definition of IA

IA was defined as the first presence of arthritis after the baseline assessment. In the AMC cohort individuals were followed over time with yearly study visits up to 7 years to evaluate the onset of IA. When IA was suspected by the study subject an interim study visit was performed at which clinically apparent arthritis (joint swelling) was assessed by two investigators (MS/MH/IC and DG). In REACH patients were followed for 2 years with assessment at 6 months, 1 year and 2 years. Development of IA was defined as either presence of an observed arthritis assessed by a trained research nurse confirmed by the rheumatologist or the use of disease modifying antirheumatic drugs (DMARDs) including biological agents or corticosteroids due to inflammatory joint diseases [8]. If subjects were lost to follow-up they were assumed as not having developed IA, since they no longer visited one of the participating clinics.

Statistical analysis

Baseline characteristics of both cohorts were analyzed using simple descriptive techniques. Diagnostic performance was assessed for developing IA within the 2 years of follow-up of the cohorts using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratio's (LR) for different cut-offs of the prediction risk score. Before evaluating the diagnostic performance the prediction rule fit was tested for discrimination and calibration. Discrimination was tested using receiver operating characteristic (ROC) curves including an area under the curve (AUC) comparable to what was done in the development phase of the prediction rule. We assessed calibration using calibration plots [9]. Although we had missing data of 2% per covariate, the combined missingness result in 20% loss of patients in the complete case analysis, therefore a multiple imputation using

20 imputed datasets was performed [10]. These results are presented. In addition we performed the analyses on the complete case dataset and on a dataset in which we set all missing values to the absence of the feature (score 0), see supplemental file 1. One individual was excluded from the analyses because of missing half the covariates of the prediction rule.
Statistical analyses were performed using STATA version 13.

Results

Cohort description

The validation cohort consisted of 154 autoantibody-positive individuals, n=77 from the AMC and n=77 from REACH. Thirty two of these individuals (21%) developed IA within one year and 47 (31%) within 2 years. Median age was 47 (IQR 27-70) years and 75% was female. Baseline characteristics are described in Table 1 for both cohorts. In most aspects the cohorts were comparable, but they differed for pain, smoking and alcohol use.

Table 1. Baseline characteristics for patients included in the AMC or REACH.

	REACH N=77	**AMC N=77**
Age, mean (SD)	47 (13)	45 (11)
Gender, n (%)	60 (78%)	55 (71%)
RF+, n (%)	59 (77%)	46 (60%)
Anti-CCP +, n (%)	43 (56%)	41 (53%)
RF + and anti-CCP +, n (%)	25 (32%)	10 (13%)
Alcohol use, n (%)	11 (15%)	45 (58%)
BMI, median (IQR)	26 (21-35)	25 (19-39)
Ever smoker, n (%)	27 (40%)	51 (66%)
VAS pain > 50*	39 (51%)	23 (30%)
TJC, median (IQR) #	3 (0-18)	2 (0-15)
Arthritis developed in 1 year, n (%)	25 (32%)	7 (9%)
Arthritis developed in 2 years, n (%)	37 (48%)	11 (14%)

Discrimination and calibration

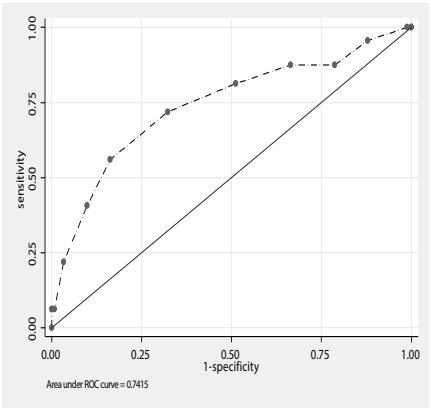
Figure 1 shows the ROC curves and the calibration plots for the prediction rule. The AUC of the ROC curve was used to illustrate the ability of the prediction rule to discriminate between patients that develop IA from those who do not. After 1 year follow-up the AUC was 0.74 (95% CI: 0. 72-0.76). After 2 years the AUC was similar, 0.73 (95% CI: 0.75-0.75). In the original cohort the AUC for the development of IA after one year was 0.81 (95% CI: 0.76 to 0.86).

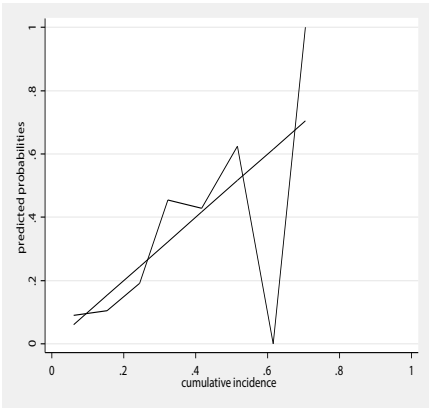
Calibration plots were used to estimate the probability for individuals of developing IA within the specified time correctly. This was done by comparing the probability predicted by the algorithm and

the observed probability within our validation cohort (figure 1). In the ideal situation the predicted values are on the diagonal, which was the case for the probabilities of less than 60% chance of developing IA. In the upper area of the plot the predicted values are quite different from the observed probabilities suggesting that there is poor model fit for subjects with high probability of developing IA.

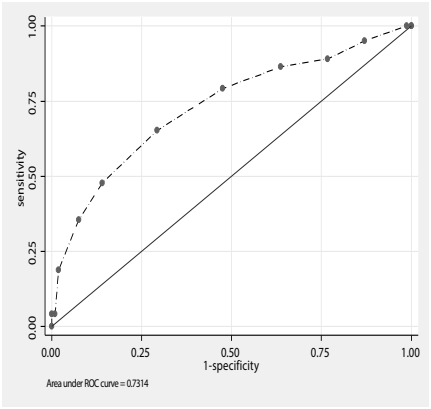
Figure 1. ROC curves (on the left) and calibration (on the right) for patients that developed IA within 1 year (1.a) and within 2 years (1.b)

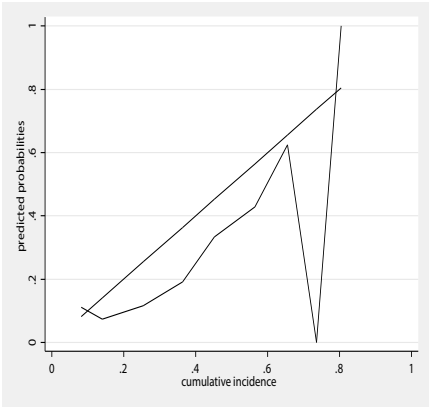
1.a





1.b





CHAPTER 5

Diagnostic performance

Diagnostic performance for each score of the model was calculated. Table 2 shows sensitivity, specificity, negative predictive values and positive predictive values. The optimum of both sensitivity and specificity was observed at a score of 7. Sensitivity here was 0.65 (95% CI: 0.51-0.79), specificity was 0.71 (95% CI: 0.61-0.80), with a PPV of 0.50 (95% CI: 0.37-0.63) and a NPV of 0.82 (95% CI: 0.74-0.90). At this cut point the positive LR was 2.2 (95% CI: 2.07-2.43). If for instance the incidence in a certain

population is 20%, using this prediction rule would result in an 44% increased risk of developing IA using a cut off of 7. The negative LR was 0.49 (95% CI: 0.45-0.54).

Table 2. Sensitivity, specificity, negative predictive values and positive predictive values including the 95% confidence intervals at each potential cut point.

Cut points	Sens	Spec	NPV	PPV
Score 1	1	0	1	0
Score 2	1	0.13 (-0.01-0.04)	1	0.31 (0.24-0.39)
Score 3	0.95 (0.88-1.01)	0.13 (0.06-0.20)	0.85 (0.67-1.04)	0.33 (0.25-0.41)
Score 4	0.89 (0.79-0.98)	0.23 (0.15-0.31)	0.82 (0.68-0.96)	0.34 (0.26-0.43)
Score 5	0.86 (0.76-0.96)	0.36 (0.27-0.46)	0.86 (0.75-0.96)	0.38 (0.29-0.47)
Score 6	0.79 (0.68-0.91)	0.52 (0.43-0.62)	0.85 (0.76-0.94)	0.43 (0.32-0.53)
Score 7	0.65 (0.51-0.79)	0.71 (0.61-0.80)	0.82 (0.74-0.90)	0.50 (0.37-0.63)
Score 8	0.48 (0.33-0.62)	0.86 (0.80-0.93)	0.78 (0.71-0.86)	0.61 (0.45-0.77)
Score 9	0.35 (0.22-0.49)	0.92 (0.87-0.98)	0.76 (0.69-0.83)	0.68 (0.50-0.86)
Score 10	0.19 (0.08-0.30)	0.98 (0.95-1,01)	0.73 (0.65-0.80)	0.81 (0.59-1.04)
Score 11	0.04 (-0.01-0.10)	0.99 (0.97-1,01)	0.70 (0.62-0.77)	0.66 (0.13-1.20)
Score 12	0.04 (-0.01-0.10)	1	0.70 (0.62-0.77)	1

Discussion

A sufficient performance was found in the external validation of the Reade prediction model of arthritis in autoantibody-positive individuals without arthritis [7]. Discrimination was slightly lower compared to the derivation cohort with an AUC of 0.73 (95% CI: 0.75-0.75) for development of IA within 2 years. We observed 35 patients with arthritis in the low risk group (0-4 points), 36 patients in the intermediate (5-6 points) and 54 patients in the high risk (7-13 points) group. The model calibrated well for the low and medium risk patients, but calibrated not well for the high risk patients resulting in an underestimation of their IA risk. In the derivation cohort no calibration data was presented. Also no single cut off value was given. We showed that a model score of 7 best discriminated patients with and without IA at 2 year follow-up with a sensitivity of 0.65 and specificity of 0.71. These results were based on data from two Dutch cohorts of auto-antibody positive individuals (AMC (n=77) and REACH (n=77)).

The cohort used for validation differed from the derivation cohort in some ways. First, the frequency of arthritis was 20% after one year and 31% after 2 years compared to 20% over 5 years in the Reade derivation cohort. This large difference is perhaps related to the REACH cohort and its inclusion criteria. The REACH did not include mere arthralgia subjects, but already incorporated some criteria indicating inflammatory complaints such as a positive family history. This might have led to a higher incidence of IA in comparison to both the derivation as well as the AMC cohort. Second, we observed differences in the distributions of our variables in comparison to the derivation cohort. For instance the AMC cohort contained a higher frequency of current and past smokers than the REACH

cohort and the derivation cohort. Also alcohol use and antibody status were different. Alcohol use was higher and anti-CCP and RF were more frequently both positive in the derivation cohort. For alcohol use this led to a loss of predictive value towards the development of IA, while it did not change the predictive value of anti-CCP and RF. This may have led to reduced performance of the prediction model in our validation cohort. Third, the sample size of our validation cohort was relatively small. Due to a lack of existing prospective cohorts with autoantibody-positive individuals without clinically apparent arthritis increasing sample size was not possible at the time [11].

Recently, another risk model was presented. It combines three clinical variables including shared epitope with power Doppler present at ultrasonography of the wrist or hands [12]. This model has not yet been validated either internally or externally. We could not validate it in our study as we have no data on ultrasonography and on shared epitope in both the REACH and the AMC cohort.

No evidence exists towards successful treatment strategies that prevent the development of IA and subsequently RA. Until the availability of preventive treatment strategies, individuals at high risk should be closely monitored in order to initiate treatment when IA becomes apparent. This will enhance the proportion of patients treated as soon as possible after symptom onset, considering the window of opportunity during which treatment may result in favourable outcome. As at the moment in daily practice it is difficult to identify arthralgia patients with a higher risk of developing IA and perhaps subsequently RA, prediction models such as the one validated here may aid. In addition, the use of such prediction models can improve research into the different phases of RA and promote the development of preventive treatment regimens for research and ultimately for clinical practice.

In conclusion, the prediction model to identify IA among seropositive arthralgia patients did not meet its derivation cohort performance. This may relate to differences in arthritis incidence and distribution of covariates. However, its performance in our cohort seems sufficient for use in practice as no alternative strategy is available for individuals with autoantibody-positive arthralgia without arthritis.

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CHAPTER Six

Periarticular osteoporosis: a useful feature in the diagnosis of early rheumatoid arthritis? Reliability and validity in a cross-sectional diagnostic study using dual-energy X-ray absorptiometry

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Abstract

Objectives

To identify regions of interest (ROIs) relevant to periarticular osteoporosis in RA with low precision error and sufficient inter-rater reliability and to test diagnostic validity for RA.

Methods

Periarticular BMD was measured using dual-energy X-ray absorptiometry (DXA). Five ROIs were defined around MCP and/or PIP joints II-V, II-IV and mid-metacarpal to mid-phalangeal. They were evaluated for precision using the root mean square coefficient of variation (RMS-CV) and the intra-class correlation coefficient (ICC) for inter-reader reliability. To test validity, established RA patients (n=25) and early arthritis patients (n=25) were compared with healthy controls (n=37) matched on sex, age and menopausal status using paired t-tests, ROC curves and scatterplots.

Results.

The RMS-CV was 0.45-1.07%. The ICC was 0.99. Mean BMDs of the five ROIs ranged from 0.321 to 0.372 g/cm^2 in established RA, from 0.321 to 0.382 g/cm^2 in early arthritis and from 0.342 to 0.401 g/cm^2 in healthy controls. Mean differences ranged from 0.012 to 0.032 g/cm^2 for established RA and from 0.023 to 0.033 g/cm^2 for early arthritis patients compared with matched controls, with $P<0.05$ for ROIs 1-5 in early arthritis and the whole hand in established RA. ROC curves indicated low discriminative power, with an area under the curve (AUC) of 0.61-0.64, and scatterplots showed great overlap between BMD values of patients and controls.

Conclusions

Periarticular BMD measured with DXA seems not to be a useful diagnostic feature due to strong overlap of BMD values between healthy controls, established RA patients and early arthritis patients.

Introduction

Due to new drugs and tightly controlled medication strategies, patients have better disease outcome, especially if treated in the early stages of the disease [1,2]. The need for early identification of RA is recognized worldwide and resulted recently in new ACR/EULAR criteria for the classification of RA [3]. This new criteria set contains the domains joints, serology, disease duration and acute-phase reactants. Patients are classified as RA if their total score is ≥ 6 points out of 10. The classification criteria perform well as diagnostic criteria in early arthritis [4]. Despite the improved criteria set, diagnostic uncertainty can still remain in patients scoring <6 points on the new criteria set.

To decrease the diagnostic uncertainty, there is a need for easy applicable and cheap imaging techniques. Early bone and cartilage changes, features of RA, could have added value in the diagnostic process. Currently, these are depicted using conventional radiography, a valid and reliable method but insensitive for early bone and cartilage changes [5]. An early feature of the disease is thought to be periarticular osteoporosis [6,7]. It can be estimated using DXR, quantitative US, CT and dual-energy X-ray absorptiometry (DXA) [8]. DXA is regarded as the reference method in generalized osteoporosis [8]. It is a valid and reliable method to measure BMD and it is cheap and has low radiation doses making it a good candidate to reduce diagnostic uncertainty in patients at risk for RA.

One of the difficulties using DXA for measuring periarticular BMD is the definition of the region of interest (ROI). It is hypothesized that the areas closest to the joint surface are more prone to BMD loss early in the disease. Previous studies tried to measure BMD in very small areas just below the joint surface, but this resulted in large measurement error [6,9-13]. BMD measured by DXA is sensitive to surface size because it is determined by bone mineral content per squared surface measure (square centimetres). With a smaller surface the impact of repositioning the hand is larger, and therefore bigger differences in BMD values occur when repeating the same measurement in a patient. To solve this, one could use a larger area like the whole hand surface, but the effect of localized periarticular osteoporosis will be diluted.

In this study, we aim to increase precision without losing the benefit of small ROIs. We, therefore, aim to (i) identify periarticular ROIs relevant to RA with a low precision error and sufficient inter-rater reliability; and (ii) to test the validity of these ROIs first by comparing extreme groups, i.e. healthy controls with patients with established RA, and secondly by comparing healthy controls with patients with early arthritis who can be regarded as patients who potentially have RA.

Methods

Precision/reliability

Precision and inter-reader reliability were assessed before using DXA in our patient sample. Five healthy adults were measured seven times to calculate the short-term precision [14]. The hand was repositioned for each measurement. To calculate the short-term precision of all ROIs and the whole hand, the formula for the root mean square coefficient of variation (RMS-CV) was used:
$\sqrt{(\sum(CV^2)/\text{number of persons})}$

To determine the inter-rater reliability, 20 patients were analysed on separate occasions by two readers (C.A. and W.J.vO.). The intra-class correlation coefficient (ICC; two way, agreement) was used to estimate inter-reader reliability of the ROIs and the whole hand measurement [15, 16].

Validity

Design

A cross-sectional, matched, case-control study was set up to assess the BMD values of periarticular regions of the hands in three groups: healthy controls, established RA and early arthritis patients. This design allowed both an extreme group comparison (healthy vs established RA) as well as evaluation among patients who would undergo the test in practice (early arthritis). If BMD values overlap in the extreme group comparison, the difference would probably not be large enough to use in daily practice where groups are not extreme. Also, an evaluation whether test results can be used to identify those with and without the target disease in practice can be done by testing in a group representative of those in whom the test will be applied. This is called a Phase 1 and Phase 2 diagnostic study; the first step to evaluate the discriminative properties of a test. It could provide data to merit the more elaborate and expensive Phase 3 diagnostic study, where the test is applied to a larger cohort of those patients that would be tested in practice [17].

Patients

Patients with established RA and a scheduled appointment in the rheumatology outpatient clinic were recruited between September 2006 and January 2008. Established RA was defined as patients with RA according to the 1987 ACR criteria existing for >1 year. This patient group was considered the extreme group for the extreme group comparison. For the evaluation of the test in those patients in whom it might be used in practice, early arthritis patients were recruited via the Rotterdam Early Arthritis CoHort (REACH) between September 2006 and October 2008. This ongoing, prospective, inception cohort study was set up in the greater Rotterdam area in July 2004. Patients were recruited either via the general practitioner (GP), or via outpatient rheumatology clinics at first consultation. Patients were included if they had at least one swollen joint or two or more joints with either pain or loss of movement with two or more of the following criteria: morning stiffness >1 h; unable to clench a fist in the morning; pain when shaking someone's hand; pins and needles in the fingers; difficulties wearing rings; difficulties wearing shoes; a family history of RA; unexplained fatigue lasting <1 year. Patients were excluded if their symptoms resulted from trauma or overuse, were >12 months, or if they were <16 years. Details of this cohort are reported elsewhere [18]. Early arthritis patients were eligible for current analysis if they had: (i) an intermediate or high probability (≥33%) of having persistent disease according to the prediction model of Visser et al [19]; (ii) arthritis of at least one of the hand joints by palpation (wrist, MCP and/or PIP joints); and (iii) were Caucasian. Patients were excluded if they ever had a fracture of the hands, had hip or hand prosthetics, if there was alcohol abuse or if they had comorbidity influencing bone metabolism, such as untreated thyroid disease.

Controls

Healthy controls were recruited to match patients on sex, age and menopausal status. The same exclusion criteria as described for patients were applied to controls. Controls were matched twice if they matched both patients in the established RA and early arthritis groups. For each patient and each control, informed consent (according to the Declaration of Helsinki) was obtained and this study was approved by the Medical Ethical Committee of Erasmus MC, Rotterdam.

Data collection

Data on risk factors for generalized osteoporosis was collected using a self-reported questionnaire. The questionnaire included medication, medical history and dietary intake of calcium. BMD of the hand, hip and lower spine were estimated using the Lunar Prodigy for DXA. Disease characteristics of patients were collected using chart data on disease duration, diagnosis, bone erosions, RF and anti-cyclic citrullinated peptide (anti-CCP).

BMD measurements of hand ROIs

The most affected hand of each patient was scanned. In case of equal involvement of both hands or no hand symptoms, the left hand was scanned. Both hands of each control were scanned and in the matched analysis the hand corresponding to the hand of the patient was chosen.

Hand BMD was assessed on the Lunar Prodigy using the hand software. The hand was placed flat on the table, with the fingers joined together. The hand was aligned using a laser light line through the styloid process of the ulna and metacarpal phalanx IV. The hand was scanned once (for 1 min and 3 s with a radiation dose of 2.0 mGy). The ROIs and the whole hand were then analysed on a single scan. The whole hand analysis was done outlining all bones of the hands including the metacarpalia and excluding the ulna and radius using the standard analysis program in the Lunar Prodigy. ROIs were chosen in the most frequently affected joints in RA in the area close to the joint surface and a surface size sufficiently large to prevent large measurement errors. ROI 1 was drawn manually along the side of the bone from the end of the distal curvature of the proximal phalanx to the end of the proximal curvature of the metacarpal bone for the MCP digits II-V (Fig. 1). ROI 2 was drawn from the end of the distal curvature of the distal phalanx to the end of the proximal curvature of the metacarpal bone for the MCPs until the PIPs of digits II-V (Fig. 1). ROI 3 was drawn identical to ROI 1, but excluded digit V and ROI 4 was drawn identical to ROI 2 excluding digit V. Finally, ROI 5 was drawn alongside the bone from mid-carpal to the middle of the phalanges for MCP II-IV. All analyses for the ROIs were done using the custom analysis program in the Lunar Prodigy. The periarticular areas of ROI 1-4 enclosed the area around the joints and were delineated where the curvature of the cortical bone started.

Statistics

Simple descriptive analyses were used to compare characteristics of RA patients, early arthritis patients and the healthy controls. To evaluate patterns in BMD values of patients and controls, scatter

plots were made. The paired t-test was used to evaluate the matched differences of the mean BMDs between cases and controls. Sensitivity and specificity for the different ROIs were calculated and shown in receiver operating characteristic (ROC) curves.

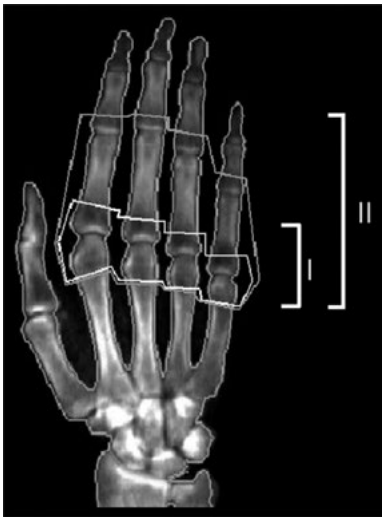


Figure 1. ROIs. ROI, shown in white region 1 (I) and in grey region 2 (II). Not shown: region 3- 5. Regions 3 and 4 were similar, but included only phalanx II, III and IV, while region 5 included the larger area from mid-phalanx to mid-carpal.

Results

Reliability

The precision expressed as RMS-CV of the ROIs and the whole hand varied from 0.74 to 1.07% for Reader 1 and from 0.45 to 0.81% for Reader 2. ROI 4 had the lowest RMS-CV in the RMS-CVs of both readers. The interreader reliability, as measured with an ICC (two-way agreement), was 0.99 for each of the ROIs and the whole hand measurements.

Validity

Subject characteristics

Twenty-five established RA and 25 early arthritis patients and 37 healthy controls were included. Demographic and subject characteristics are described in Table 1. The mean age of menarche was 13 years for both patients and controls. Fifteen patients were post-menopausal, eight with established RA and seven with early arthritis. Four patients had thyroid disease, but all were euthyroid.

Table 1. Characteristics of patients and controls

Characteristics	Established RA (n=25)	Early arthritis (n=25)	Controls (n=37)
Age, mean (s.d.), years	53 (13)	52 (12)	52 (12)
Female %	72	68	68
Height, mean (s.d.), cm	170 (7.6)	170 (8.9)	173 (8.5)
Weight, mean (s.d.), kg	78 (12.2)	74 (16.9)	76 (12.1)
BMI, means (s.d.)	27 (5.2)	25 (5.5)	25 (2.8)
Thyroid disease*, n	0	4	0
Years since menopause, median (range)	11 (1-24) (n=8)	11 (1-19) (n=7)	8 (3-23) (n=11)
Smoking current %	8	32	13
Smoking past %	70 (mv=20)	53 (mv=8)	53 (mv=5)
Dietary calcium, intake, median (range), mg/week	3770 (154-9901)	3718 (480-7264)	3666 (385-7612)
Disease characteristics			
Diagnosis			
RA, %	100	52	NA
Monoarthritis, %	NA	16	NA
Polyarthritis, %	NA	16	NA
PsA %	NA	8	NA
SpA, %	NA	4	NA
OA, %	NA	4	NA
Current DMARD use, %	100	88#	NA
Current steroid use, %	4#	52#	NA
Current calcium medication, %	4	44#	NA
Current vitamin D use, %	4	44#	NA
Bone erosions, %	52	20	NA
Disease duration, median (range), months	57 (13-258) (mv=1)	5 (0-18) (mv=2)	NA
DAS-28, mean (s.d.)	2.79 (1.18) (mv=4)	3.53 (1.27) (mv=1)	NA
RF positive, %	56	48	NA
Anti-CCP positive, %	48 (mv=2)	52	NA
ESR at baseline, median (range)	15 (1-38)	12 (2-75) (mv=1)	NA
Sharp-van der heijde score, median (range)	9 (0-92)	4 (0-44)	NA

* Patients had either been hypothroid in the past or had had a struma. #Medication was no longer than 2 weeks. mv: missing values on this specific item; NA: not applicable

In the early arthritis group, 52% of the patients were diagnosed as RA (n=13). DMARDs were used by all the established RA patients and 88% (n=22) of the early arthritis patients. Use of steroids, calcium or vitamin D was highest in early arthritis patients, 52, 44 or 44%, respectively. In this group, the exposure to medication (DMARDs, steroids, calcium or vitamin D) was <2 weeks, as they were recruited for this study immediately after diagnosis.

Figure 2. Scatterplot of unmatched BMD values of ROI 1 for all patients (X) and controls ( ).

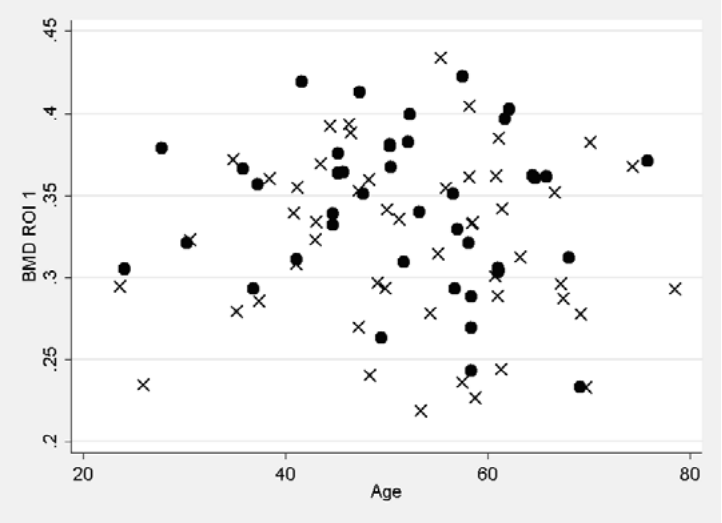
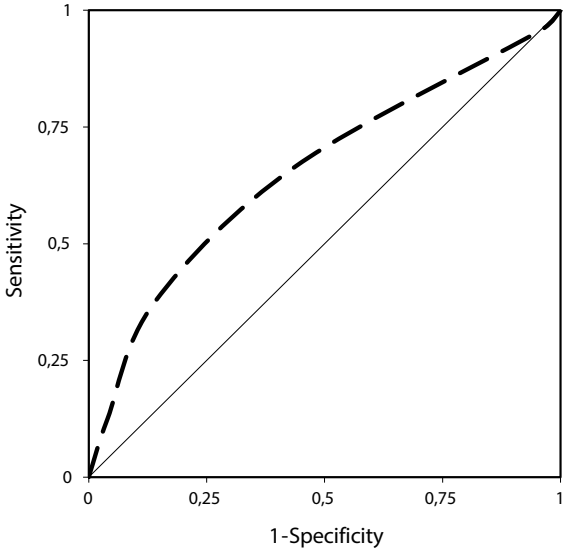


Figure 3. ROC curve for ROI 1 in early arthritis (AUC = 0.62)



BMD measurements

Unmatched BMD means are given per group for each ROI and the whole hand in Table 2. The mean BMDs of the different ROIs ranged from 0.321 to 0.372 g/cm2 in the established RA group, from 0.321 to 0.382 g/cm2 in the early arthritis group and from 0.342 to 0.401 g/cm2 in the healthy controls. The

mean differences for established RA compared with their matched controls ranged from 0.012 to 0.032 g/cm2 and were only significant in the whole hand measurement (P<0.05). In the early arthritis patients, ROIs 1-5 showed significant differences with the matched controls (Table 3). The mean differences ranged from 0.023 to 0.033 g/cm2 for these patients with their matched controls.

Table 2. BMD-unmatched mean (s.d.)

Region of interest	Established RA (n=25)	Early arthritis (n=25)	Controls (n=37)
ROI 1, g/cm^2	0.321 (0.047)	0.321 (0.058)	0.342 (0.048)
ROI 2, g/cm^2	0.334 (0.044)	0.338 (0.057)	0.353 (0.046)
ROI 3, g/cm^2	0.334 (0.048)	0.334 (0.058)	0.358 (0.050)
ROI 4, g/cm^2	0.347 (0.047)	0.351 (0.058)	0.368 (0.047)
ROI 5, g/cm^2	0.372 (0.051)	0.382 (0.060)	0.401 (0.047)
Whole hand, g/cm^2	0.387 (0.048) (n=24)	0392 (0.062)	0.420 (0.050)
Lumbar spine, g/cm^2	0.953 (0.128)*	1.171 (0.160)	1.228 (0.146)
Hip, g/cm^2	0.966 (0.141) (n=24)	0.939 (0.107)	1.003 (0.123) (n=36)

* One outlier was removed from the analysis of lumbar spine BMD

Table 3. One sample t-test on matched differences between BMD patients and controls

Region of interest	Established RA (n=25)	Early arthritis (n=25)
ROI 1, mean diff. (s.d.), g/cm^2	-0.015 (0.061)	-0.028 (0.052)*
ROI 2, mean diff. (s.d.), g/cm^2	-0.012 (0.053)	-0.023 (0.054)*
ROI 3, mean diff. (s.d.), g/cm^2	-0.017 (0.066)	-0.033 (0.060)*
ROI 4, mean diff. (s.d.), g/cm^2	-0.016 (0.060)	-0.024 (0.057)*
ROI 5, mean diff. (s.d.), g/cm^2	-0.022 (0.062)	-0.026 (0.056)*
Whole hand, mean diff. (s.d.), g/cm^2	-0.032 (0.061) (n=24)	-0.021 (0.078)

* p<0.05

To illustrate patterns in BMD values of patients and controls, the rough data of ROI 1 were plotted in Fig. 2. The scatter plot showed that the BMD values for patients overlapped those of the controls. The other ROIs and separate plots for established RA and early arthritis showed similar patterns of overlap in values of patients and controls (data not shown).

To evaluate discriminative power of the different ROIs, ROC curves were made. One of the ROC curves is demonstrated in Fig. 3. It indicated low discriminative power, as did all other ROC curves. The corresponding area under the curve (AUC) for these ROC curves varied from 0.61 to 0.64.

Discussion

Despite high measurement precision of the ROIs defined in this study to evaluate periarticular BMD loss in the hand, we could not demonstrate that unmatched BMD values distinguished between healthy

controls and established RA or early arthritis. This means that simple application of hand DXA without correcting for age, seks and post-menopausal status is likely not to improve diagnostic certainty in patients at risk for RA, despite significant differences in periarticular BMD shown in matched analysis. Previous studies have suggested that a decrease in periarticular BMD could have diagnostic value, based on significant differences between RA patients and healthy controls [6, 9, 20-22]. These studies did not evaluate the diagnostic properties of DXA using a specific cut-off. The average BMD values that were presented suggest that also in these studies DXA would not discriminate between healthy controls and early arthritis or RA patients if a cut-off had been applied. However, determination of periarticular osteoporosis might still be used as a diagnostic tool. Two longitudinal studies with early arthritis patients who were later on diagnosed with RA showed BMD values at baseline comparable with those of the other diagnostic groups, while over time BMD decreased more rapidly for the patients later on diagnosed with RA compared with the other diagnostic groups [10, 12]. So it might be that the raw BMD value in itself does not have strong discriminatory properties, but its change over time might have.

Measuring early changes in BMD over time requires a very small measurement error to prove that the observed change is larger than the smallest detectable change. DXA is less likely a candidate instrument for this due to its precision error of 1%. Quantitative US (QUS) or digital X-ray radiogrammetry (DXR) might be better candidates, with measurement errors as low as 0.50% for QUS and 0.25% for DXR [23, 24]. Both have shown promising results in regard to predictive value for early diagnosis, with the more promising results for DXR [25, 26]. These small precision errors are sufficiently small to use these techniques in the diagnostic workup for RA if measured twice in a short period, for instance 3 months.

Another possibility of detecting RA early might be by measuring markers of bone damage instead of using imaging techniques. Measurement of the serum Receptor activator of nuclear factor kappa-B ligand/osteoprotegerin (RANKL/OPG) ratio might be a candidate approach. RANKL promotes bone damage through up-regulation of osteoclast formation and is increased in RA [27]. OPG decreases the effect of RANKL, but is down-regulated in RA. The RANKL/OPG ratio provides information on the severity of RA and on bone damage. It has shown promising results in predicting development of bone damage [28]. Therefore, measurement of serum RANKL/OPG ratio might also be valuable as a diagnostic tool for RA and it might also inform us on disease severity at the moment of diagnosis.

This study has certain strengths and weaknesses. Its strength is first that we included established RA as well as early arthritis patients, enabling us to evaluate BMD loss in an extreme group as well as patients who are likely to undergo the test in practice. This last patient set allows evaluation of BMD in a group including not only patients with RA but also those with arthritis due to other causes. This is an important step in the evaluation of a diagnostic test [17]. Secondly, we were able to reduce the precision error by creating sufficiently large periarticular ROIs, without the need to estimate the whole hand BMD. This increased our chance to pick up small differences in periarticular BMD early in the disease course.

Weaknesses of our study could be, first, our relatively small sample size, which may change the BMD estimates when replicating this study with a larger sample size. However, this design was intended to evaluate the need for a larger diagnostic study. As there was a great overlap of BMD values in both healthy and diseased individuals, increasing the sample size would lead to more significant results, but the BMD values on an individual level would not change by enlarging the sample. Thus, it would still be difficult to use periarticular BMD as a diagnostic testbased on DXA estimates, and therefore gathering a larger sample would not be cost-effective. Secondly, the DXA measurements might be influenced by the presence of synovitis. From measuring BMD in the spine, we know that inaccuracies up to 20% may occur due to obesity [29]. Synovitis creates a small increase in the amount of soft tissue around the joint that may affect the BMD assessments in a similar way as obesity does. However, to what extent is unknown. Thirdly, we did not correct for the presence of bone erosions. In case of bone erosions on the side of the joint, the area of eroded bone will not be picked up by the DXA. As DXA is a surface measure, this will not directly affect the BMD reading. We tested this hypothesis by randomly excluding portions of bone. BMD, however, remained the same (data not shown). If an erosion is more central in the bone, the erosion will be regarded as complete BMD loss by DXA in that particular area, and therefore decrease the periarticular BMD. This would only increase differences between BMD of patients vs controls, and therefore improve diagnostic power. This is not a problem in a diagnostic study, although it would be for an aetiological study.

In conclusion, periarticular BMD measured crosssectionally with DXA is not a useful diagnostic feature to distinguish RA patients from healthy people, due to the wide distribution in BMD values. This resulted in strong overlap between healthy controls, established RA patients and early arthritis patients. This gives rise to a discussion about the use of periarticular osteoporosis, measured by DXA, as a diagnostic criterion for RA early in the disease course.

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CHAPTER

Seven

Diagnostic performance of the ACR/EULAR 2010 criteria for rheumatoid arthritis and two diagnostic algorithms in an early arthritis clinic (REACH)

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Abstract

Introduction

An ACR/EULAR task force released new criteria to classify rheumatoid arthritis at an early stage. This study evaluates the diagnostic performance of these criteria and algorithms by van der Helm and Visser in REACH.

Methods

Patients with symptoms ≤12 months from REACH were used. Algorithms were tested on discrimination, calibration and diagnostic accuracy of proposed cut-points. Two patient sets were defined to test robustness; undifferentiated arthritis (UA) (n=231) and all patients including those without synovitis (n=513). The outcomes evaluated were methotrexate use and persistent disease at 12 months.

Results

In UA patients all algorithms had good areas under the curve 0.79, 95% CI 0.73 to 0.83 for the ACR/EULAR criteria, 0.80, 95% CI 0.74 to 0.87 for van der Helm and 0.83, 95% CI 0.77 to 0.88 for Visser. All calibrated well. Sensitivity and specificity were 0.74 and 0.66 for the ACR/EULAR criteria, 0.1 and 1.0 for van der Helm and 0.59 and 0.93 for Visser. Similar results were found in all patients indicating robustness.

Conclusion

The ACR/EULAR 2010 criteria showed good diagnostic properties in an early arthritis cohort reflecting daily practice, as did the van der Helm and Visser algorithms. All were robust. To promote uniformity and comparability the ACR/EULAR 2010 criteria should be used in future diagnostic studies.

Introduction

Recently an American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) task force released new classification criteria for rheumatoid arthritis (RA) at an early stage [1]. These criteria might also have diagnostic value early in the disease process although this has not yet been evaluated. Early diagnosis is important to improve patient outcome by early treatment to prevent joint damage and functional impairment [2].

The previous classification criteria for RA (the 1987 ACR criteria) proved inadequate in the early stages of disease [3,4]. This led to the development of other diagnostic algorithms [5,6]. These algorithms showed good diagnostic performance and identified patients at an early stage of the disease [7-9].

Diagnostic algorithms tend to be overoptimistic in their capabilities when only tested in the population they were derived from [10]. For instance, if a high erythrocyte sedimentation rate (ESR) is an important predictor for RA but in the derivation cohort by chance only a few patients had a high ESR, the data-driven way in which these algorithms are build will not identify this predictor. Therefore before use in practice the discriminative abilities of such algorithms should be tested in another cohorts with similar patients (similar incidence rate). In addition, the robustness of algorithms to variation of incidence rates can be tested in cohorts with different previous disease probabilities [11-13].

We aim to evaluate the diagnostic performance of the ACR/EULAR 2010 criteria and two diagnostic algorithms simultaneously to predict methotrexate use or persistent disease in the Rotterdam Early Arthritis Cohort (REACH). In addition, we will test robustness after defining two patient sets in the same cohort resulting in different previous probabilities of developing RA.

Methods

Diagnostic algorithms

Three diagnostic algorithms were evaluated. The first is the new ACR/EULAR 2010 criteria set [1]. The other two, the algorithms by van der Helm and the one by Visser, are existing, well-known models [5,6].

Validation cohort

Clinical data used were from REACH. This ongoing, prospective, inception cohort study was set up in the greater Rotterdam area in July 2004. Patients were recruited either via their general practitioner, or via the outpatient rheumatology clinic of three hospitals at first consultation. Patients were included in case of one or more swollen joint or, in the absence of joint swelling, if they had two or more joints with pain or loss of movement with two or more of the following criteria: morning stiffness for more than 1 h; unable to clench a fist in the morning; pain when shaking someone's hand; pins and needles in the fingers; difficulties wearing rings or shoes; a family history of RA; unexplained fatigue for less

than 1 year. Patients were excluded if their symptoms resulted from trauma or overexertion, were for over 12 months, or if they were younger than 16 years.

A trained research nurse at the REACH clinic took a standardised history and conducted a physical examination at baseline, 6 and 12 months, including blood and urine samples. For the current analysis data from baseline and 1 year were used. Physical examination included the measurement of tender and swollen joints, using a 44 joint count. Laboratory variables included IgM-rheumatoid factor (ELISA), anti-cyclic citrullinated peptide (Elia CCP on immunoCAP 250; Phadia Freiburg, Germany), C-reactive protein (local standards) and ESR (local standards). x-Rays of hands and feet were assessed for bony erosions at baseline. For a detailed description of REACH, see Geuskens et al [14].

Statistical analyses

To asses overall performance the prediction algorithms were tested on discrimination and calibration [15]. Discrimination is the ability of an algorithm to differentiate correctly between patients with and without the disease. Calibration reveals the ability to estimate the probability of the diagnosis for individuals correctly by comparing the probability predicted by the algorithm and the observed probability. To evaluate discrimination receiver operating characteristic curves, including corresponding areas under the curve (AUC), were calculated. Calibration was evaluated using calibration plots and the Hosmer–Lemeshow test [15]. The latter indicates good calibration if a non-significant result appears. To assess diagnostic performance of the algorithms sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were estimated at cut-points proposed for treatment initiation among patients at risk of RA. For the ACR/EULAR 2010 criteria and Visser algorithm a score of 6 or more [1,16] was used and for van der Helm a score of 8 or more [5] was used. To test robustness this analysis was repeated among all patients included in REACH. This group had a lower previous disease probability by a case-mix of synovitis and inflammatory joint complaints without synovitis. Synovitis was defined as joint swelling.

As a classifier for correct diagnosis two outcomes were evaluated at 1 year: the use of methotrexate and persistent disease, defined as synovitis present at physical examination after 1 year, or the use of disease-modifying antirheumatic drugs (DMARD) including biological agents. Patients with a definite alternative diagnosis such as gout were not classified as persistent disease. A complete case analysis was done.

Results

Validation cohort

Up to 31 October 2008, 875 patients were referred to REACH and had 1-year follow-up. One hundred and 13 patients did not fulfill the inclusion criteria and 31 patients were lost to follow-up at baseline (figure 1). Patients used in the development of the ACR/EULAR 2010 criteria were excluded (n=216) [1]. Table 1 reports baseline characteristics of all patients (n=513). Patients had a mean age of 50 years,

73% were women and the median symptom duration was 106 days (range 1–366 days). At baseline 48% (n=246) presented with synovitis. After 1 year, 148 of 513 used methotrexate, of whom 22 did not have synovitis at baseline, and 231 of 513 patients had persistent disease, of whom 59 did not have synovitis at baseline.

Figure 1. Flow diagram of inclusion and follow-up in the REACH.

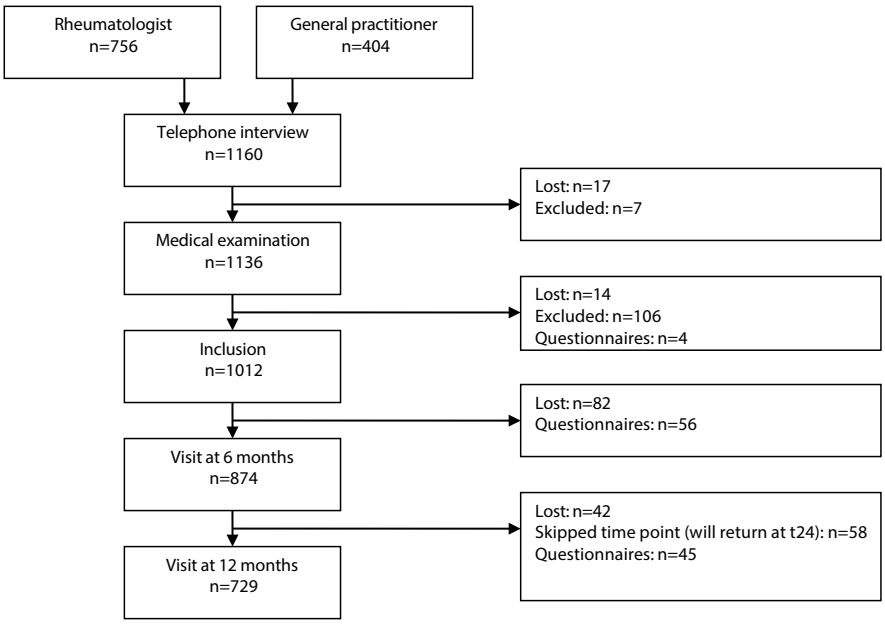

Table 1 Patient characteristics for each patient set

	UA (n=231)	All patients (n=513)
Women %	68	73
Age, years (mean, SD)	53 (14)	50 (14)
SJC (median, range)	4 (1–38)	0 (0-50)
TJC (median, range)	7 (0-42)	6 (0-42) mv=2
RF positive (%)	35%	26%
Anti-CCP positive (%)	28% mv=6	19% mv=2
ESR, mm/h (median, range)	18 (1-103) mv=7	14 (0-103) mv=15
CRP, mg/l (median, range)	6 (1-180) mv=16	5 (1-180) mv=40
Erosions (%)	9% mv=4	4% mv=9
RA according to 1987 ACR criteria	29% mv=3	14% mv=5
RA according to 2010 ACR/EULAR criteria	45% mv=12	58% mv=6
Persistent arthritis at 1 year	45% mv=9	71% mv=3

ACR, American College of Rheaumatology; CCP, cyclic citrullinated protein; CRP, C-reactive protein; ESR, erythocyte sedimentation rate; EULAR, European league Against Rheumatism; mv, missing values; RA, Rheumatoid arthritis; RF rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; UA, undifferentiated arthritis.

Discrimination

Table 2 shows AUC of each diagnostic algorithm for both outcomes. In undifferentiated arthritis (UA) patients (n=231) the AUC for methotrexate use were comparable, with overlapping 95% CI, 0.79 (95% CI 0.73 to 0.83) for the ACR/EULAR 2010 criteria, 0.80 (95% CI 0.74 to 0.87) for the van der Helm algorithm and 0.83 (95% CI 0.77 to 0.88) for the Visser algorithm. For persistent disease the AUC were 0.77 (95% CI 0.71 to 0.85) for the ACR/EULAR 2010 criteria, 0.78 (95% CI 0.71 to 0.85) for the van der Helm algorithm and 0.77 (95% CI 0.71 to 0.83) for the Visser algorithm. In all patients (n=513) the AUC were comparable for both outcomes, with slightly better performance of the van der Helm algorithm; 0.88 (95% CI 0.84 to 0.91) and 0.83 (95% CI 0.79 to 0.87).

Table 2. Area under the reciever operating characteristic curves with 95% CI for each algorithm and each patient set

	ACR/EULAR 2010	Van der Helm	Visser
Outcome methotrexate use			
UA patients	0.79 (0.73 to 0.85)	0.80 (0.74 to 0.87)	0.83 (0.77 to 0.88)
All patients	0.79 (0.75 to 0.83)	0.88 (0.84 to 0.91)	0.80 (0.76 to 0.85)
Outcome persistent disease			
UA patients	0.77 (0.71 to 0.85)	0.78 (0.71 to 0.85)	0.77 (0.71 to 0.83)
All patients	0.74 (0.70 to 0.78)	0.83 (0.79 to 0.87)	0.74 (0.70 to 0.79)

UA, undifferentiated arthritis

Calibration

Calibration plots of all diagnostic algorithms are shown in figure 2. In UA patients (n=513) calibration was worse than in all patients, although the Hosmer–Lemeshow test was not significant for any of the calibration plots. All algorithms calibrated well in all patients (n=513), confirmed by the Hosmer–Lemeshow test.

Evaluating diagnostic performance using proposed cut-points

To identify patients in need of treatment proposed cut-points were tested in UA patients. The ACR/EULAR criteria showed a sensitivity of 0.74 (95% CI 0.65 to 0.82) and a specificity of 0.66 (95% CI 0.54 to 0.76), with the cut-point of 6 or higher using methotrexate as a classifier for correct diagnosis (table 3). The Visser algorithm and the van der Helm algorithm had a lower sensitivity, 0.47 and 0.59 for the Visser algorithm for both outcomes and 0.08 and 0.10 for the van der Helm algorithm. Specificity was higher: 0.93 for the Visser algorithm and 1.0 for the van der Helm algorithm.

Figure 2. Calibration plots for UA patients for the outcome MTX use (a) and persistent disease (b). Perfect calibration is achieved when the observed probabilities match the derived probabilities, resulting in a calibration line on the diagonal.

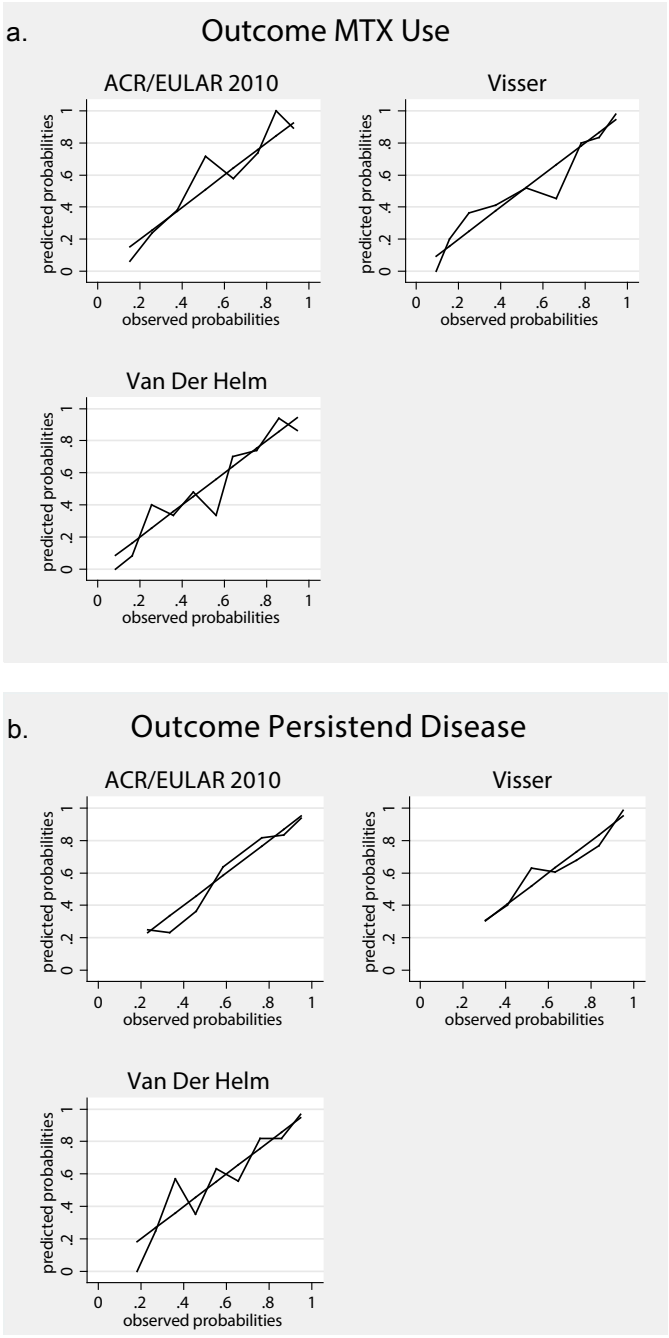

Table 3. Sensitivity, specificity, and PPV and NPV at the proposed cut-points in UA patients

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Methotrexate use				
ACR/EULAR 2010 criteria	0.74 (0.65 to 0.82)	0.66 (0.54 to 0.76)	0.76 (0.67 to 0.83)	0.63 (0.52 to 0.73)
Van der Helm algorithm	0.10 (0.05 to 0.17)	1.0 (0.95 to 1.0)	1.0 (0.74 to 1.0)	0.43 (0.35 to 0.50
Visser algorithm	0.59 (0.50 to 0.68)	0.93 (0.85 to 0.97)	0.92 (0.84 to 0.92)	0.62 (0.53 to 0.71)
Persistent disease				
ACR/EULAR 2010 criteria	0.69 (0.61 to 0.76)	0.72 (0.59 to 0.83)	0.87 (0.80 to 0.92)	0.46 (0.35 to 0.56)
Van der Helm algorithm	0.08 (0.05 to 0.14)	1.0 (0.93 to 1.0)	1.0 (0.75 to 1.0)	0.27 (0.21 to 0.34)
Visser algorithm	0.47 (0.39 to 0.55)	0.93 (0.84 to 0.98)	0.95 (0.87 to 0.99)	0.40 (0.31 to 0.48)

ACR, American College of Rheumatology; EULAR, European league Against Rheumatism; NPV, negative predictive value; PPV, positive predictive value; UA, undifferenttiated arthritis.

The PPV is the probability that a patient has the disease if the test is positive. The van der Helm algorithm had the highest PPV; 1.0. The NPV is the opposite probability and was highest for the ACR/EULAR criteria with 0.63 for methotrexate use and 0.46 for persistent disease, slightly higher than the Visser algorithm.

Discussion

The results of our study show that the new ACR/EULAR 2010 criteria could aid diagnostics in early arthritis patients. They had good overall performance, with a sufficiently high AUC and good performance of the proposed cut-point of 6 for persistent disease, which could be considered RA. The other algorithms performed well when tested for discriminatory properties (AUC and calibration), although the van der Helm algorithm failed to detect cases at the proposed cut-point. To promote uniformity and comparability of studies we would suggest using the ACR/EULAR 2010 criteria in future diagnostic studies.

The cut-point of 6 in the ACR/EULAR 2010 criteria was well chosen and showed good diagnostic performance, even though it was not intended for diagnostic purposes [1]. Choosing a cutpoint is a trade-off between harm of treatment in non-cases (overtreatment) and harm of no treatment in cases (undertreatment) [13, 17]. Ideally a cut-point has a high sensitivity to prevent undertreatment and a high specificity to prevent overtreatment. However, a high specificity is often accompanied by a low to moderate sensitivity and vice versa. For the ACR/EULAR 2010 criteria both sensitivity and specificity were approximately 70%. Using this cut-point of 6 to start treatment, in this study 30% of persistent patients would not be treated, whereas 30% of the non-persistent patients would have been. Lowering the cut-point to 4 increases sensitivity to 0.92 at the cost of specificity (0.33). Increasing it to 7 had a sensitivity of 0.53 and a specificity of 0.85. Perhaps creating a low, intermediate and high-risk group for disease using dual cut-points would enable treatment with different intensities.

The cut-point of 6 was chosen using the AUC of three cohorts, including our own. In this study the AUC for methotrexate use, 0.79, was similar to that in the derivation article (0.66–0.82), indicating consistency. It was also similar (0.77) for persistent disease. It could be argued that this is a direct result of the use of our data in the derivation cohort. However, the decision to use 6 as cut-point was based on expert opinion and two other cohorts. Furthermore, patients included in the derivation of the ACR/EULAR 2010 criteria were removed from analyses.

The strengths of our study include the heterogeneity of patients' subsets to test robustness of the algorithms and simultaneous evaluation of three diagnostic algorithms in one study sample. We showed that the ACR/EULAR criteria and both algorithms were robust in a case-mix of synovitis and non-synovitis patients. Calibration was good for all algorithms, but not perfect. Calibration and robustness have not been evaluated before by others, but discrimination was. The van der Helm algorithm showed AUC of 0.82–0.88 and the Visser algorithm an AUC of 0.70, both similar to the AUC in the present study [7-9].

This study should be interpreted in the light of current developments in diagnostic research in RA. Current diagnostic studies within RA are faced with defining a suitable outcome. We defined two outcomes; methotrexate use similar to the definition of the ACR/EULAR 2010 and persistent disease (either synovitis or DMARD use at 12 months) [1]. This may have led to misclassification in two ways. Patients could be classified as true positive because they were still using methotrexate or other DMARD at 12 months, whereas in fact some patients may not need treatment. Likewise, patients may have had episodes of arthritis with no episode or DMARD use at 12 months, while later on they developed persistent arthritis.

In conclusion, the new ACR/EULAR 2010 criteria showed good diagnostic properties in an early arthritis cohort reflecting daily clinical practice, as did the van der Helm and Visser algorithms. All were robust. To promote uniformity and comparability we would suggest using the ACR/EULAR 2010 criteria in future diagnostic studies.

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CHAPTER

Eight

Do we need to lower the cut point of the 2010 ACR/EULAR classification criteria for diagnosing rheumatoid arthritis?

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Abstract

Objective

In part of the patients who do not fulfil the 2010 ACR/EULAR classification criteria at first consultation (<6 points) arthritis persists. To be able to identify more patients with rheumatoid arthritis, we evaluated the effect of lowering the cut point of the 2010 criteria.

Methods

We included early arthritis patients from the Rotterdam Early Arthritis Cohort (REACH) with at least one joint with clinical synovitis and symptoms less than 1 year with no other explanation for their symptoms. Demographic and clinical characteristics of each patient were recorded at baseline. Patients were classified as case or non-case at 1 year follow-up by the definition used in the development of the 2010 criteria (methotrexate initiation). To assess diagnostic performance of the 2010 criteria sensitivity and specificity at each cut point was determined.

Results

We included 557 patients in our analysis. After 1 year follow-up 253 patients (45%) were classified as case (methotrexate use). In the group of patients who scored 0-5 points (n=328) 98 patients (30%) were classified as case (methotrexate use). Sensitivity and specificity of the 2010 criteria using the cut point of 6 were 61% and 76% respectively. With the cut point of 5, sensitivity would increase to 76% and specificity would decrease to 68%.

Conclusion

By lowering the cut point of the 2010 criteria from 6 to 5 points, we were able to identify 15% more rheumatoid arthritis patients at the cost of 8% more false-positive patients.

Introduction

Recently, the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis (RA) were developed to facilitate research in earlier stages of the disease. The 2010 criteria also facilitate optimal use of the window of opportunity by starting disease modifying drugs at an earlier time point [1]. The 2010 criteria assign the risk or probability of developing RA on a continuous score (from 0 to 10). A score of ≥6/10 is needed to classify a patient as having definite RA.

Some of the patients in whom arthritis persists over time do not fulfil the 2010 criteria (<6/10 points) at first consultation [2]. In unselected early arthritis cohorts, the proportion of missed persistent arthritis patients can increase to almost 40%, which is likely to reflect the case-load of daily practice [3]. As Krabben et al showed neither ACPA nor the Leiden prediction rule are able to identify which individual patients will be missed by the 2010 criteria [4]. Therefore, we need another way to identify patients whose arthritis will persist.

The developers of the 2010 criteria suggest that there is scope for using other cut points for different purposes [1]. In this study we evaluated which cut point of the 2010 criteria would enable us to identify more early rheumatoid arthritis patients among early inflammatory arthritis patients at first consultation.

Methods

Patients

For the present study we included early arthritis patients from the Rotterdam Early Arthritis Cohort (REACH) with at least one joint with clinical synovitis and symptoms for less than 1 year with no other explanation for their symptoms. Patients were recruited via their general practitioner, or via the outpatient rheumatology clinic. Patients were included in REACH in case of one or more swollen joints. Patients were excluded if their symptoms resulted from trauma or overuse, if their symptoms were present for over 12 months, or if they were younger than 16 years. For a detailed description of REACH, see Alves et al [5].

Each patient was assigned a score from 0 to 10 points using the 4 domains of the 2010 criteria: i) joint involvement; ii) serology; iii) acute-phase reactants; iv) symptom duration [1]. Demographic and clinical characteristics of each patient were recorded at baseline, 6 months and 12 months. Data collection included a detailed medical examination (swollen joint count, tender joint count), laboratory variables (ACPA, RF, ESR), diagnosis and medication used.

Written informed consent was obtained from the participants. The study was approved by the local medical ethic committee.

Case definition

Patients were classified as case (true-positive patients) or non-case after 1 year follow-up by the definition used in the development of the 2010 criteria [1]. This definition includes the use of methotrexate (MTX) after 1 year. If a patient had to stop MTX due to side-effects, and was assigned another DMARD, it was also considered a case. If no MTX was used and no other classifiable disease was present after 1 year follow-up the patient was regarded a non-case.

Statistical analysis

Discriminative performance of the 2010 criteria in relation to the case definition was determined by calculating the receiver operating characteristic (ROC) curve. Sensitivity and specificity were calculated for each cut point (0-10 points). To obtain information on potential other clinical characteristics that could help improve the diagnostic performance we tested differences between cases and non-cases among the patients with <6/10 points using the independent T-test or Wilcoxon-Mann-Whitney test depending on the distribution of the data. Frequencies were compared using a Chi-square test. Analyses were done using STATA 12.0.

Results

In REACH we identified 726 early arthritis patients. At baseline we excluded 169 patients with another classifiable disease, such as gout, psoriatic arthritis and systemic diseases. Consequently, in 557 patients the 2010 criteria could be applied of which 328 patients (69%) obtained a score from 0 to 5.

Sensitivity and specificity 2010 criteria

The ROC curve was calculated for the 2010 criteria in relation to MTX use in the total study population (0-10 points; n=557) (Figure 1). The area under the ROC curve (AUC) was 0.79 (SE 0.02). From this curve sensitivity and specificity for each score were determined.

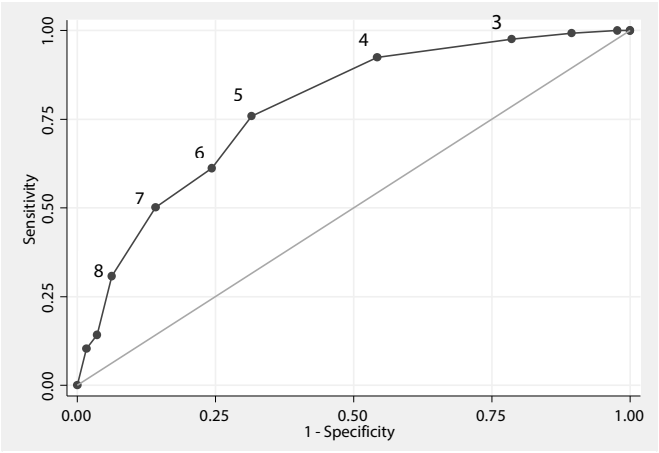
Sensitivity and specificity of the 2010 criteria using the cut point of 6 were 61% and 76% respectively. With the cut point of 5, sensitivity increased to 76% and specificity decreased to 68%. Among patients with 5 points (n=59) 22 patients (37%) would be false-positively classified as RA. After 1 year follow-up the diagnosis of these false-positive patients was osteoarthritis (n=2) or remitting oligoarthritis/polyarthritis (n=20) .

Patients with 0-5 points

In the patients with 0-5 points (n=328) 98 patients (30%) used MTX (case) after 1 year follow-up. Figure 2 shows the distribution of cases and non-cases over the 2010 score. Patients with a higher score on the 2010 criteria showed a higher frequency of MTX use after 1 year.

Characteristics of patients with MTX (case; n=98) were compared with patients who did not use MTX (non-case; n=230) (Table 1). Patients who used MTX tended to have more tender and swollen joints and higher ESR values, but showed no differences on the other characteristics such as rheumatoid factor and ACPA positivity.

Figure 1 The receiver operator characteristic curve, and sensitivity (Sens) and specificity (Spec) for the 2010 criteria and MTX use (n = 557)



Cut point	Sens (%)	Spec (%)
0	100	0
1	100	2
2	99	11
3	98	21
4	92	46
5	76	68
6	61	76
7	50	86
8	31	94
9	14	96
10	10	98

Figure 2 Outcome after 1 year follow-up. Number of cases (MTX) versus non-cases for each score on the 2010 criteria (0-10 points).

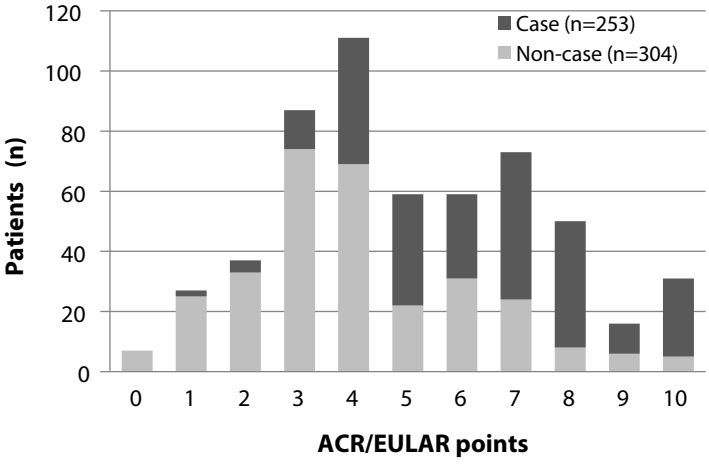


Table 1: Baseline characteristics of patients with 0-5 points who used MTX after 1 year follow-up (case) and of those patients who did not use MTX (non-case)

	Case (MTX use) (n=98)	Non-case (n=230)	p-value
Women (%)	69	67	0.667
Age, years (mean, SD)†	54 (16)	50 (16)	0.051
SJC (median, IQR)*	5 (3-7)	2 (1-4)	<0.001
TJC (median, IQR)*	9 (4-12)	5 (2-10) mv=3	<0.001
RF positive (%)	7	5	0.494
ACCP positive (%)	2 mv=13	5 mv=12	0.370
ESR (median, IQR)*	24 (12-39) mv=1	13 (6-25) mv=23	<0.001
CRP (median, IQR)*	6 (3-35) mv=16	5 (2-16) mv=50	0.032
Morning stiffness, min (median, IQR)*	60 (30-140) mv=20	45 (30-90) mv=78	0.034
DAS44 score (mean, SD)†	4.6 (1.0) mv=3	3.8 (1.1) mv=27	<0.001
Symptom duration, months (median,IQR)*	3 (2-6)	3 (1-5) mv=6	0.029
MCP symmetry (%)	62	40 mv=2	<0.001
PIP symmetry (%)	46	36 mv=2	0.077
Wrist symmetry (%)	39	19 mv=2	<0.001
MTP symmetry (%)	12	7 mv=2	0.164

SD = standard deviation, IQR = interquartile range, mv = missing values, † independent T-test, *Wilcoxon-Mann-Whitney test

Discussion

By lowering the cut point of the 2010 criteria from 6 to 5 points, we were able to identify 15% more rheumatoid arthritis patients at a cost of 8% more false-positive patients. If these reclassified patients had started DMARD therapy after first consultation, 2/3 of the patients would have received optimal early treatment, while the other 1/3 of the patients might not have needed this treatment, as their symptoms were not related to the presence of RA. Each rheumatologist has to weigh the benefit of early treatment in true-positive rheumatoid arthritis patients against the harm of treatment in oligoarthritis/polyarthritis and osteoarthritis patients, i.e. the false-positive patients. Balancing the benefit and harm of treatment depends on the safety profile of the DMARDs and the quality of life lost if true-positive patients are left untreated [6]. In general, the safety profile of the different DMARDs is regarded as acceptable in the treatment of RA [7], but it is not clear whether this also holds for arthritis patients who score 5 points. Treatment in arthritis patients with 5 points seems beneficial [8], but none of these studies have evaluated the potentially negative effect of treatment in the false-positive patients. In terms of quality of life, Geuskens et al found no difference in health-related quality of life between RA patients and non-RA patients [9], which might imply that treatment in arthritis patients with 5 points will improve their quality of life. Data is lacking on the presence of off-days mentioned by patients, which affects worker productivity due to the side-effects of medication.

The characteristics of the patients with 0-5 points (n=328) differed little between those with and those without MTX. Although swollen and tender joint counts differed, the differences were not strong enough to be used as an additional diagnostic criterion (data not shown). This is in accordance with findings of Krabben et al [4]. To reduce over-treatment in false-positive patients and to be more certain which patients could start early DMARD treatment, it might be beneficial to add other (imaging) biomarkers that distinguish true positive patients from false-positive patients at an earlier stage [10-12]. Nevertheless, lowering the cut point from 6 to 5 points would be a more feasible way to identify more persistent arthritis patients.

Our study has certain strengths and limitations. The REACH dataset was one of the early arthritis cohorts included in the pooled analysis to develop the new criteria for RA [1,13]. The cut point of 6 was chosen using the AUC of three cohorts, including REACH. When we removed those patients (n=184) from our analysis, the results were similar (data not shown). However, external validation of our results in another early arthritis cohort is recommended. The strength of our study includes the selection of patients, which was not biased towards RA. In REACH, no limits were set regarding the minimal number of swollen joints required, and the sample represents patients in an early phase of their disease (median duration of symptoms of 3 months).

In conclusion, by lowering the cut point of the 2010 criteria, we identified more rheumatoid arthritis patients in whom early treatment could have been initiated. This could have led to better patient outcomes.

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CHAPTER Nine

General Discussion

Early recognition of RA has become important in recent years as early treatment improves the outcome of RA [1-3]. Distinguishing disease features are lacking in the early phase and the insidious onset makes it challenging to recognize, especially in primary care where the incidence is low and GPs deal with many other musculoskeletal disorders [4-8].

In the current thesis three main research aims were formulated to improve early recognition of patients in the earliest phases of RA both in primary care and secondary care. The studies addressing issues in primary care are described in part one. The main aim of these studies was:

- to assess delays in referral in an early arthritis cohort (EAC) and to find ways to improve these delays.

Part two includes the studies relating to secondary care. Two main aims were formulated:

- to establish the occurrence of IA (inflammatory arthritis) in patients with arthralgia and how to recognize patients that develop IA.
- to evaluate different diagnostic tests, including the 2010 ACR/EULAR criteria, to diagnose RA early among patients with IA.

To address these aims data from the Rotterdam Early Arthritis CoHort (REACH) were used [9]. Patient eligible for REACH comprised of those that had IA according to the GP and those that had 2 painful joints and at least 2 predefined inflammatory characteristics (e.g. morning stiffness, problems wearing shoes). This resulted in a cohort that included a wide variety of inflammatory arthritis patients, with both classified and unclassified diagnosis and also patients that presented with mere arthralgia. This allowed studying patients with a wide variety of inflammatory joint complaints.

Part one - Challenges of early recognition in primary care

The first part of this thesis focuses on early recognition in primary care. We first studied the time interval from symptom onset to first visit at the EAC. About half of the RA patients was seen in a 12 week interval regarded necessary for an optimal effect of early DMARD treatment [submitted]. Compared to historical data the RA patients in REACH had a substantial reduction of delay [10-12]. In the Leiden EAC 31% of the RA patients were seen within the 12 week interval, which means that the implementation of the REACH led to a gain of 19% [13]. To further improve delays the research group from Leiden implemented a new strategy; the Early Arthritis Recognition Clinic (EARC) [14]. In the EARC GPs could refer without the use of criteria, doubts on synovitis at physical examination was sufficient to refer. Referral delay was reduced to a median of 11 weeks, which was similar to our results [14]. However, this means that half of the patients still have a substantial delay and therefore cannot benefit from treatment in the very early stage of clinical disease.

To better understand why delays occur in primary care, we assessed factors associated with swift referral from the GP [submitted]. We looked at patient characteristics and symptoms at presentation.

Swift referral - within 12 weeks of symptom onset- was associated with an elevated CRP. This is a typical feature of acute severe onset of IA, which was also observed by vd Linden et al in the Leiden EAC [13]. None of the clinical symptoms or patient characteristics were associated. In addition, we tested the accuracy of the assessment of synovitis by the GP and its association with swift referral [submitted]. REACH allowed GPs to send in patients with and without synovitis. Compared to the synovitis evaluation by the rheumatologist a patient with synovitis according to the GP had a 50% chance to have IA. A patient without synovitis according to the GP had almost 40% chance to be diagnosed as IA [submitted]. This suggests that physical examination by GPs is not optimal, creating room for improvement of early recognition of IA. A fundamental problem for the limited skill to recognize IA is most likely the low incidence of both IA and RA in primary care, leading to a lack of expertise on the part of the GP in recognizing synovitis. As synovitis is a key item in many referral guidelines as well as in most referral criteria for existing EACs early referral may be hampered by the requirement of the presence of synovitis [15].

To reduce referral delays we proceeded to develop a referral tool without the prerequisite of the identification of synovitis upon physical examination [submitted]. To this end the characteristics (demographic, clinical and self-reported complaints) of patients with a definite IA as diagnosed by the rheumatologist were compared to the patients in whom IA was absent. A broad array of candidate variables (n=51) that could be related to the presence of IA was used. We used statistical methodology from prediction rule development to fit a model that did not exceed the number of variables to events in a ratio of 1:10. It resulted in a weighted score – varying from 0-11 - using the following variables: gender, squeeze test of hands and feet, acute onset, duration between 3 - 6 months, absence of fatigue and the following self-reported joint problems: restricted movement, painful, swollen or red or warm joints. The optimum score above which patients should be referred was 6 points. The tool showed promising results with an AUC of 0.80 (95% CI: 0.76-0.85) and an adjusted AUC of 0.77 (95% CI: 0.72-0.82) after internal validation using bootstrap.

Both studies described in the first part of this thesis focused on the challenge of early recognition in primary care. Delays in our EAC were analyzed in addition to variables associated with swift referral. EAC's such as REACH are already interventions aimed at improving early referral providing easily assessable facilities for evaluations of referred patients with inflammatory musculoskeletal complaints. Compared to historical data the REACH - using referral criteria based on tacit knowledge about inflammatory characteristics - showed a reduction of delay to about 12 weeks. These results are similar to the EARC where referral was simply based on doubts on the part of the GP [14]. Combining these results leads to the conclusion that it is important to at least provide a means of referral that is easily accessible to both patients and GPs. Such strategies can potentially lead to additional costs, due to increased referral of patients without - a risk of - IA. We attempted to provide more accurate referral criteria based on our data to reduce the number of patients that do not have IA and to increase the likelihood of having IA. The referral tool that we created only requires simple variables from history taking and a squeeze test of hands and feet. It does not require the skill to identify synovitis at physical examination which makes it an improvement compared to existing guidelines and recommendations.

Despite its simplicity it has shown potential at internal validation, which makes it a viable option for use in GP practices. Of course it needs external validation [16]. Preferably while simultaneously validating existing guidelines and recommendations to allow a comparison between them.

Up to now several other strategies were developed to improve delays in primary care. These include educational programs, combined consultations with rheumatologists, the implementation of EAC's and expert opinion based referral guidelines and recommendations. All strategies developed to date were described in a systemic literature review by Villeneuve et al [15]. These strategies were not evaluated for their effect on delay, although it is conceivable that these interventions can influence delays positively [15]. Possible drawbacks of these interventions include that many require physical examination of synovitis, lack of formal testing for their effect on delay and are time-consuming increasing costs. For instance, educational programmes might help GPs to better examine and recognize synovitis. But this takes time and effort of both GPs and rheumatologists. Furthermore, the gained skills cannot be maintained due to the low incidence of IA in GP practices which would lead to loss of the acquired skill, making training less feasible. Another option would be to implement an EAC. We showed that this is feasible as it can decrease delays and it does not require the skill of recognizing synovitis. Similar results are seen in the EARC. At the moment, the implementation of such a cohort is the only feasible option with proven effects in lowering delays.

Further research is needed to improve early recognition of IA in primary care. With 50 symptoms and signs tested in our study it is not likely that recognition of simple clinical signs or symptom will reduce delay. With technological advances in cytomics, metabolomics, genomics and genetics new biomarkers may become available [17-20]. To implement these in primary care they need to be cheap and fairly accurate to further improve early recognition of IA in primary care. At the moment though no new and cheap biomarkers are available [21,22]

Validity

The treats on internal validity (selection bias and information bias) and external validity (generalizability) of the results are discussed below.

Selection bias

There is no general accepted definition of inflammatory musculoskeletal complaints, therefore referral criteria for REACH were based on tacit knowledge of rheumatologists and GPs about inflammatory joint symptoms. This resulted in a definition including synovitis and in absence of synovitis the presences of 2 painful joints and 2 other inflammatory criteria. Patients with inflammatory joint disease could have been missed as they could have presented with one joint. As RA is a poly-articular disease the data might be skewed towards poly-articular disease. Selection bias could also have occurred due to the implementation of the inflammatory criteria. The implication on the patient selection is unclear as patients tend to present with a wide variety of symptoms. We could have missed patients because we missed inflammatory components in our referral criteria.

Information bias

Recall bias is an issue when studying delay. Information on dates concerning the occurrence of the initial complaints and the first visit to the GP were gathered based on the recollection of patients. Differential misclassification (being a synovitis case or not) seems not a major issue here as most patients were asked this information before they were diagnosed.

External validity

Application of our results in daily clinical practice depends on the patients in which they are applied to. Patients were selected towards an inflammatory profile. This was already discussed in the item on selection bias, but the use of the referral criteria could also lead to threats on external validity as our population is not completely representative of the patient population with inflammatory complaints in primary care. A specific issue in external validity is the application of the internally validated referral tool. Whether this tool is robust to other selection criteria remains unclear until data is available from other populations.

Optimism is a pivotal aspect in the external validity of the referral tool [16]. It refers to the fact that statistical models fit best in their development cohort. Optimism results from specific distributions of variables in cohorts. For instance, a variable such as smoking can be a strong predictor for a certain outcome in one cohort, but have a lesser association in another cohort due to smoking less. This leads to a strong influence in a prediction model in the first hypothetical cohort whereas if the same technique to derive a prediction model were used in the second fictional cohort the influence of smoking would be less or perhaps even absent. To reduce the influence of optimism on a prediction model, external validation should be done [16]. If optimism is a problem, adjustments of the model should be made to improve its generalizalibity [16]. Unfortunately, for our referral tool external validation was not possible at the moment as no similar cohort exists. Internal validation was done using bootstrap techniques, but external validation should still be performed [23]. Preferably this should occur in a cohort including patients directly from primary care to assess its value in the setting it is intended for. Furthermore, if external validation is done simultaneously for the existing tools and referral guidelines it would provide a direct comparison helping GPs to choose the best referral tool or guideline.

Part two - Challenges of early recognition in secondary care

Part two of this thesis focuses on challenges of early diagnosis in secondary care in which 2 main topics were studied: 1) recognizing IA among arthralgia and; 2) early diagnosis of RA.

Recognizing IA among arthralgia

Many patients present with arthralgia without arthritis at first consultation in the outpatient rheumatology clinic. Although its frequency has never been subject to research, discussion with

rheumatologists suggest this can be over half of their new patients depending on their practice setting. Although most of these patients with arthralgia will not develop IA or RA, some patients will develop clinically apparent synovitis later on [24,25]. However, if these patients are sent back to their GP without further monitoring this could result in a lost opportunity of early treatment.

The one year incidence of IA in the patients with mere arthralgia was determined in REACH [submitted]. We observed that 15 % of artralgia patients in REACH developed IA. Factors associated with this were ACPA, RF and ESR of which ACPA had the strongest association (OR 6.31, 95% CI 3.07-13.00) [submitted]. About one third of the ACPA positive patients developed arthritis in the subsequent year [submitted]. In the RF and ACPA negative patients the incidence was 12% in which ESR was the only item associated with incident IA.

The ACPA or RF positive artralgia patients were further studied by applying a previously developed prediction model that aimed to identify patient at risk for synovitis over time if they were positive for anti-CCP and/or RF [submitted]. This external validation is presented in Chapter Five. Discrimination was reasonable with an AUC of 0.74 (95% CI: 0.72-0.76), which was lower than the original AUC of 0.81 (95% CI: 0.76 to 0.87) presented in the original study [26]. Comparing predicted values with observed values using calibration plots showed some underestimation of the predicted risk in higher risk populations. In practice this would mean that the model would underestimate the risk among patient that had a risk of over 60%.

The data presented on arthralgia patients suggest that part of these patients would benefit from active surveillance by the rheumatologists to detect incident arthritis in due time. This would allow for early treatment providing optimal patient outcomes. It also would enable the study of very early rheumatoid arthritis hopefully nipping the disease in the bud. Guidance for which patients should be monitored is not straightforward. For patients that are ACPA or RF positive one may consider the application of the previous developed prediction model [26]. It would be helpful to have more data on it is performance in other cohort of patients. In our external validation we saw that some of the predictor variables were differently distributed compared to the development cohort causing the model to perform less optimally. For RF and ACPA negative patients identifying patient that would benefit from active surveillance is more difficult. Only higher levels of ESR was associated with incident IA in this group but the discriminatory power is not sufficient to be used in daily clinical practice as prognostic marker. Further research is required to evaluate whether the addition of imaging techniques or other biomarkers would help early identification of whom would benefit from active surveillance. New biomarkers such as anti-CarP might identify ACPA and RF negative patients at risk for RA. Anti-CarP has already shown promising results in this population [27], but more research to confirm these result are necessary. Imaging techniques such as MRI and ultrasound have proven to be more sensitive at identifying synovitis than physical examination [28]. However, the clinical relevance of these findings need to be confirmed before they can be used in daily practice [28].

Validity

Selection bias

Patients that were included from REACH were subject to selection towards inflammation due to the eligibility criteria used for the study. Within the arthralgia patients this probably influenced the estimate of the one-year incidence of inflammatory arthritis. As we selected patients that fulfilled our definition of inflammatory complaints one should not apply these figures to patients from the general population or primary care as it would overestimate the incidence of arthritis. In secondary care the incidence of IA in arthralgia patients is likely to be similar as patients seen in secondary care are also already selected towards a higher probability of IA by their GPs.

Information bias

In the external validation of the prediction model not all variables were available as used in the development cohort. Part of the data had to be obtained from medical charts. This data was not collected in a systematic manner as information in medical charts are the result of the routines of the specialists who use these charts. This measurement error occurred in both arthritis cases and non-cases (non-differential misclassification). This could possibly dilute the association but without affecting its direction.

Early diagnosis of RA among patients with IA

In the last decade there has been substantial discussion about the features that are used to diagnose RA. Since their introduction, the ACR 1987 classification criteria have been used for diagnostic purposes although they were developed for homogenous patient selection in trials [29]. They comprised of features that were part of late stage disease such as noduli and erosions [29]. This limited their use in early disease. In response new classification criteria were introduced in 2010 based on prediction model methodology, see table 1 [30]. The formation of these classification criteria was a result of a trend towards early diagnosis of RA. This trend already led to the development of two prediction models from the Leiden EAC [31,32].

Both existing prediction models from the Leiden EAC and the 2010 ACR/EULAR criteria were validated in this thesis to evaluate their potential diagnostic performance [33]. A good discriminatory performance was shown for all models with AUCs above 0.79 for each model and a good calibration of predicted risk values compared to observed risk values. The use of the cut off values as provided by the models resulted in sensitivity and specificity around 0.6 to 0.8 for the Visser model and the 2010 ACR/EULAR criteria. The van der Helm model showed sensitivity of 0.1 causing false negatives and as a consequence delayed treatment. Due to a very high specificity though, the AUC was comparable to both other models.

The outcomes used to assess the three models including the 2010 ACR/EULAR criteria were composite outcomes [30,33]. One of the outcomes used was the start of medication - namely MTX -, the other was persistent IA - one of the characteristic features of RA -. The use of these composite

outcomes was necessary as no golden standard exists and as one would like to prevent a circular reasoning as a result of using classification criteria. The same problem existed for the derivation study of the 2010 ACR/EULAR criteria, where they also used the same composite outcomes. Although these outcome measures are needed, they are not completely independent of the items used in the 2010 ACR/EULAR criteria. Items such as an increase of number of affected joints are also commonly used by rheumatologists to identify patients with RA and to start DMARDs.

Although the 2010 ACR/EULAR criteria perform well, the classification criteria developer chose a cut off in which RA patients could still be misclassified as non-RA [30]. This is of course the tradeoff between sensitivity and specificity [34]. In a systematic literature review the showed a sensitivity of 0.8 and a specificity of 0.6 [35]. To improve risk stratification in misclassified patients several strategies might be considered such as improving imaging modalities or adjusting the cut off. As conventional radiography is insensitive for early bone and cartilage changes one may consider to use other imaging modalities to identify early bone and cartilage changes associated with RA [36]. Periarticular osteoporosis is one of the early changes in bones which could be assessed by Dual X-ray Absorptiometry (DEXA) [37]. Although an accurate technique was developed in our study using DEXA, overlap between values among those with RA, IA and healthy controls prevented its diagnostic use [38]. Another way is to increase sensitivity of the 2010 ACR/EULAR criteria by using a different cut off value. A cut off of 5 instead of 6 was evaluated [submitted]. This resulted in 14% more patients with persistent IA at risk for RA, at the cost of 8% more false-positive patients. The advantage over adding another test is that no additional test cost are involved.

The final aim of this thesis was to evaluate different diagnostic tests to diagnose RA early among patients with IA. New techniques and tests are welcome to further differentiate patients with RA from patient that have self-limiting IA. Currently a lot of work is done in the field of imaging, although both MRI and ultrasound have their advantages and disadvantages [28]. Maybe a combination with current clinical markers and other lab based biomarkers may help to reach that goal [39].

Validity

The studies to improve early recognition of RA in secondary care were done in the REACH. As with the other studies the referral criteria to REACH needs to be taken into account when interpreting these results. The study on the cut off might have affected the results of the different cut off value for the 2010 ACR/EULAR criteria as it can influence the trade-off between sensitivity and specificity.

Both studies conducted with the 2010 ACR/EULAR criteria are discussed simultaneously as for both the same threat to validity described previously could have influenced the results, namely optimism. Optimism could have influenced the results in because a part of the REACH cohort was used in the development-cohort of the 2010 ACR/EULAR criteria [30]. However, results of both studies were unchanged when analyzed without these patients suggesting that the effect of optimism was minimal. Furthermore, most EACs available at the time were used for the construction of these criteria, which makes independent validation difficult.

Table 1. The 2010 classification criteria for rheumatoid arthritis [30].

2010 classification criteria*	Score
Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints	2
4-10 small joints	3
> 10 joints (at least one small joint)	5
Serology	
Negative RF and anti-CCP	0
Low positive RF or low positive anti-CCP	2
High positive RF or high positive anti-CCP	3
Acute phase reactants	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms	
Duration < 6 weeks	0
Duration ≥ 6 weeks	1

* The target population for these classification criteria are patients who have at least one joint with definite synovitis with the synovitis not better explained by another disease.

Harm and benefit of early detection of IA patients

Early identification of patients with classified IA such as RA, PsA and AS has become a paradigm in rheumatology since the introduction of effective therapy [ref]. By omitting late features of the disease for early diagnosis using features that exist when the disease is not yet fully visible, a new challenge emerged. The change to falsely classify a patient as RA. Benefits of diagnosing and subsequently treating patients are numerous and include less joint damage, a better functional status, better chances at maintaining work and [1-3]. However, studies on harm in those falsely diagnosed are lacking. Side effects of DMARD medication are regarded benign by physicians, but no data exist whether patients view this in a similar way. Also little is known about the psychological impact of the diagnosis of a chronic inflammatory disease when in fact a self-limiting IA explains the complaints. The discussion on harm and benefit of early diagnosis and treatment should also include financial considerations. Both under and overtreatment can lead to more costs. In the case of the referral tool additional costs can be incurred due to additional diagnostic tests in patients that would otherwise not be tested. This thesis though cannot provide sufficient information to weight these issues on harm/benefit. At least it could lead to the realization that even if a patient is diagnosed with RA in an early phase, clinicians should bear in mind that their diagnosis may need revision after time as perhaps patients are misdiagnosed. In addition it may also lead to a discussion on the harm and benefit of early treatment in analogy to the discussion on the early identification of carotid stenosis in asymptomatic patients [40].

Recommendations based on this thesis

Below recommendations for both daily practice and research are listed based on the research described in this thesis.

Recommendations for daily practice

In primary care

1. We need continuous awareness among GPs.
2. We should provide facilities for early referral of patients suspected of IA or RA either using specific referral criteria or the professional judgment of the GP.

In secondary care

1. For ACPA and/or RF positive patients with arthralgia a prediction model could be used to select those patients that would benefit from active surveillance.
2. For patients with arthralgia in the absence of ACPA and RF a high ESR may indicate IA. If no other explanation exists for this high ESR, these patients might benefit from active surveillance.

Recommendations for further research

Primary care

1. The referral tool to aid early recognition of IA in primary care presented in this thesis requires external validation. This preferably should be done simultaneously with existing guidelines and referral tools based on expert opinion.
2. Additional research should be aimed at finding and testing new and cheap biomarkers that could be easily applied to large populations with low prevalence of IA or RA.

Secondary care

1. Diagnostic trials should be performed to establish the impact of using the 2010 ACR/EULAR criteria
2. In secondary care new biomarkers and imaging techniques are needed to improve risk stratification in patients that do not fulfill the RA classification criteria, but are at risk of RA.

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CHAPTER

Ten

Summary

Samenvatting

Summary

Rheumatoid arthritis (RA) is an autoimmune disorder which is characterized by joint inflammation eventually causing joint destruction and potentially severe disability. This can be prevented if treatment is initiated in the earliest phase of the disease. Therefore, early recognition of RA has become important in recent years which is challenging as distinguishing disease features are lacking in the early phase. Furthermore, the insidious onset makes it challenging to recognize, especially in primary care where the incidence is low and GPs deal with many other musculoskeletal disorders.

In the current thesis three main research aims were formulated to improve early recognition of patients in the earliest phases of RA both in primary care and secondary care. The studies addressing issues in primary care are described in part one. The main aim of these studies was:

- to assess delays in referral in an early arthritis cohort (EAC) and to find ways to improve these delays.

Part two includes the studies relating to secondary care. Two main aims were formulated:

- to establish the occurrence of inflammatory arthritis (IA) in patients with arthralgia and how to recognize patients that develop IA.
- to evaluate different diagnostic tests, including the 2010 ACR/EULAR criteria, to diagnose RA early among patients with IA.

To address these aims data from the Rotterdam Early Arthritis CoHort (REACH) were used. Patient eligible for REACH comprised of those that had IA according to the GP and those that had 2 painful joints and at least 2 predefined inflammatory characteristics (e.g. morning stiffness, problems wearing shoes). This resulted in a cohort that included a wide variety of inflammatory arthritis patients, with both classified and unclassified diagnosis and also patients that presented with mere arthralgia. This allowed studying patients with a wide variety of inflammatory joint complaints.

Part one - Challenges of early recognition in primary care

The first part of this thesis focuses on early recognition in primary care. In **chapter 2** we studied the time interval from symptom onset to first visit at the REACH. Patients were seen with a median delay of 13 weeks in REACH. In the subsample of patients with RA the median delay was 12 weeks. However, the effect of treatment is optimal when it is started within a 12 week interval after symptom onset. This means that despite the implementation of an EAC, namely the REACH, 50% of patients experience a delay longer than 12 weeks with an adverse effect on their outcome. To better understand why these delays occur in primary care, we assessed factors associated with swift referral from the GP - within 12 weeks of symptom onset-. We looked at patient characteristics and symptoms at presentation. Swift referral was only associated with an elevated CRP. None of the other clinical symptoms or patient characteristics were associated, including the identification of synovitis by the GP.

In **chapter 3** we set out to develop a referral tool without the prerequisite of the identification of synovitis upon physical examination. First, we tried to further confirm that the assessment of

synovitis by the GP was not sufficiently accurate to use as an item in referral. We had information on the identification of synovitis by the GP of 346 patients. Of the 135 patients referred with synovitis according to the GP, about half had synovitis according to the rheumatologist. Of the 211 patients without synovitis according to the GP about 40% had synovitis according to the rheumatologist. This may suggest that identification of synovitis by GPs is not optimal. A fundamental problem for the limited skill to recognize IA is most likely the low incidence of both IA and RA in primary care, leading to a lack of expertise on the part of the GP in recognizing synovitis. As synovitis is a key item in many referral guidelines as well as in most referral criteria for existing EACs early referral may be hampered by the requirement of the presence of synovitis. The development of referral guidelines that do not include synovitis as a prerequisite may improve early referral of IA or RA further. Therefore, in **chapter 3** we proceeded to develop a referral tool without the prerequisite of the identification of synovitis upon physical examination. We compared the characteristics (demographic, clinical and self-reported complaints) of patients with a definite IA as diagnosed by the rheumatologist to the patients in whom IA was absent. We used statistical methodology from prediction rule development to fit a model that did not exceed the number of variables to events in a ratio of 1:10. It resulted in a weighted score – varying from 0-11 - using the following variables: gender, squeeze test of hands and feet, acute onset, symptom duration between 3 - 6 months, absence of fatigue and the following self-reported joint problems: restricted movement, painful, swollen or red or warm joints. The optimum score above which patients could be best referred was 6 points. The tool showed promising results with an AUC of 0.80 (95% CI: 0.76-0.85) and an adjusted AUC of 0.77 (95% CI: 0.72-0.82) after internal validation using bootstrap. Despite its simplicity it has shown potential at internal validation, which makes it a viable option for use in GP practices. Of course it needs external validation.

Part two - Challenges of early recognition in secondary care

Part two of this thesis focuses on challenges of early diagnosis in secondary care. Two main topics were studied: 1) recognizing IA among arthralgia and; 2) early diagnosis of RA.

Recognizing IA among arthralgia

Many patients present with arthralgia without arthritis at first consultation in the outpatient rheumatology clinic. Most of these patients with arthralgia will not develop IA or RA, but some patients will develop clinically apparent synovitis later on. If these patients are identified and monitored they have an opportunity of early treatment.

In **chapter 4** we determined the one year incidence of IA in the patients with mere arthralgia in REACH. We observed that 15% of arthralgia patients in REACH developed IA. Factors associated with this development were ACPA, RF and ESR. ACPA had the strongest association (OR 6.31, 95% CI 3.07-13.00). In the subsample of RF and ACPA negative patients the incidence was 12%. ESR was the only item associated with incident IA in this subsample.

The ACPA or RF positive arthralgia patients were further studied in **chapter 5**. A previously developed prediction model that aimed to identify patients at risk for synovitis was validated in ACPA or RF positive arthralgia patients. Seventy-seven ACPA or RF positive arthralgia patients from the REACH were combined with 77 patients from the AMC to provide a validation cohort with a reasonable sample size. Discrimination was reasonable with an AUC of 0.74 (95% CI: 0.72-0.76), which was lower than the original AUC of 0.81 (95% CI: 0.76 to 0.87) presented in the original study. Comparing predicted values with observed values using calibration plots showed some underestimation of the predicted risk in higher risk populations. In practice this would mean that the model would underestimate the risk among patient that had a risk of over 60%. Sensitivity and specificity were optimal at a model score of 7, with a sensitivity of 0.65 (95% CI: 0.51-0.79) and a specificity of 0.71 (95% CI: 0.61-0.80).

The data presented on arthralgia patients suggest that it would be possible to identify patients for active surveillance by the rheumatologists to detect incident arthritis which would allow for early treatment providing optimal patient outcomes.

Early diagnosis of RA among patients with IA

The ACR 1987 classification criteria have been used for diagnostic purposes although they were developed for homogenous patient selection in studies and are comprised of features of late stage disease such as noduli and erosions. This limits its use in early disease. In response, new classification criteria were introduced in 2010. The formation of these classification criteria was a result of a trend towards early diagnosis of RA which had already led to the development of two prediction models from the Leiden EAC.

Both existing prediction models from the Leiden EAC and the 2010 ACR/EULAR criteria were validated in **chapter 7** to evaluate their potential diagnostic performance. A good discriminatory performance was shown for all models with AUCs above 0.79 for each model and a good calibration of predicted risk values compared to observed risk values. The use of the cut off values as provided by the authors of the models resulted in sensitivity and specificity around 0.6 to 0.8 for the Visser model and the 2010 ACR/EULAR criteria. The van der Helm model showed sensitivity of 0.1 causing false negatives and as a consequence delayed treatment. Due to a very high specificity though, the AUC was comparable to both other models.

Although the 2010 ACR/EULAR criteria perform well, the cut off chosen could still lead to misclassification of patients as non-RA. To improve risk stratification in misclassified patients several strategies might be considered such as improving imaging modalities or adjusting the cut off. As conventional radiography is insensitive for early bone and cartilage changes one may consider to use other imaging modalities to identify early bone and cartilage changes associated with RA. Periarticular osteoporosis is one of the early changes in bones which could be assessed by Dual X-ray Absorptiometry (DEXA). We developed an accurate technique to measure periarticular osteoporosis using DEXA in **chapter 6**. To this end healthy test subjects were measured. After we established an accurate technique we proceeded to test the diagnostic validity for RA. Early IA patients, RA patients

were measured and compared to healthy controls matched on sex, age and menopausal status. Mean differences in bone mineral density (BMD) were significantly different between early IA patients, RA patients and their matched healthy controls. However, overlap between values among those with RA, IA and healthy controls prevented the diagnostic use of measuring periarticular osteoporosis using DEXA. We did not test other imaging techniques in the scope of this thesis, but we did test another way to increase sensitivity. We tested the use of a different cut off value for the 2010 ACR/EULAR criteria. This was evaluated in **chapter 8**. Sensitivity and specificity were calculated for all possible cut off values in patients from the REACH cohort. At a cut off of 5 this resulted in an increase of sensitivity with 14%, meaning 14% more patients with persistent IA at risk for RA would be identified. As specificity decreased with 8%, this means that the increase of sensitivity would be at the cost of 8% more false-positive patients. The advantage of this strategy is that no additional test costs are involved.

In **chapter 9** our results are summarized and discussed considering methodological issues, current literature and implications for daily practice and further research.

Samenvatting

Reumatoïde artritis (RA) is een auto-immuunziekte die gekarakteriseerd wordt door gewrichtsontstekingen die kunnen leiden tot schade aan gewrichten en uiteindelijk tot ernstige beperkingen. Dit kan voorkomen worden wanneer behandeling gestart wordt in de eerste fase van de aandoening. Om deze reden is vroege herkenning van RA belangrijk geworden in de laatste jaren. Aangezien er weinig onderscheidende symptomen zijn in deze eerste fase van RA is vroeg herkenning moeilijk. Daarbij maakt het wisselvallige begin van de aandoening het moeilijk om het te onderscheiden, vooral in de eerste lijn waar de incidentie laag is en waar er vele andere musculoskeletale aandoeningen zijn om het van te onderscheiden.

In dit proefschrift zijn drie voornaamste onderzoeksdoelen geformuleerd om vroege herkenning van patiënten in de vroegste fases van RA te herkennen in de eerste lijn en in de tweede lijn. De studies in de eerste lijn zijn beschreven in deel 1. Het voornaamste onderzoeksdoel van deze studie was:

- Het beschrijven van de vertraging van verwijzing naar de REACH en het vinden van manieren om dit te verbeteren

Deel 1 betreft studies met betrekking tot de tweede lijn. Hiervoor zijn twee onderzoeksdoelen geformuleerd:

- Vaststellen hoe vaak inflammatoire artritis (IA) voorkomt bij patiënten met artralgie en het beter herkennen van de patiënten met artralgie die IA ontwikkelen
- Evalueren van verschillende diagnostische methoden, inclusief de 2010 ACR/EULAR criteria, om RA vroeg te diagnosticeren bij patiënten met IA.

Om deze onderzoeksdoelen te bestuderen zijn gegevens uit het Rotterdam Early Arthritis CoHort (REACH) gebruikt. Patiënten konden door huisartsen naar de REACH verwezen worden wanneer ze volgens de huisarts IA hadden of wanneer ze 2 pijnlijke gewrichten hadden met minstens 2 tevoren gedefinieerde inflammatoire kenmerken (bijvoorbeeld ochtendstijfheid of problemen met het dragen van schoenen). Dit leidde tot een cohort waarbij patiënten zijn geïncludeerd met een spectrum van patiënten met IA, variërend van patiënten zonder diagnose tot patiënten met een classificeerbare aandoening, maar ook patiënten zonder IA met artralgie. Dit heeft het mogelijk gemaakt om patiënten te onderzoeken met een verscheidenheid aan inflammatoire klachten.

Deel 1 – Uitdagingen van vroege herkenning voor de eerste lijn

Het eerste deel van dit proefschrift betreft vroege herkenning in de eerste lijn. In **hoofdstuk 2** hebben we het tijdsinterval tussen de eerste symptomen en het eerste bezoek aan de REACH onderzocht. Er was een mediane vertraging tot het eerste bezoek bij de REACH van 13 weken. In de subpopulatie van RA patiënten bedroeg dit 12 weken. Echter, het effect van behandeling is optimaal wanneer dit gestart wordt in de eerste 12 weken. Dit betekent dat ondanks het implementeren van een vroege artritis cohort, namelijk de REACH, 50% van de patiënten een vertraging oplopen langer dan 12

weken wat kan leiden tot een nadelige uitkomst. Om beter te begrijpen waarom deze vertragingen optreden in de eerste lijn, zijn factoren onderzocht die geassocieerd zijn met een snelle verwijzing – binnen 12 weken - van de huisarts. Patient karakteristieken en symptomen bij presentatie zijn onderzocht. Een snelle verwijzing was alleen geassocieerd met een verhoogd CRP. Geen van de andere karakteristieken waren hiermee geassocieerd. Ook het vaststellen van een artritis door de huisarts was niet geassocieerd.

In **hoofdstuk 3** was het doel om een verwijsmodel te ontwikkelen waarbij het vaststellen van artritis geen vereiste was. Voordat we dit deden, wilden we bevestigen dat het vaststellen van artritis door de huisarts niet voldoende is om te gebruiken als een item in een verwijsmodel. We hadden gegevens over het vaststellen van artritis door de huisarts bij 346 patiënten in de REACH. 135 patiënten werden verwezen door de huisarts met artritis. Dit werd in ongeveer in de helft van de patiënten bevestigd door de reumatoloog. Van de 211 patiënten die werden verwezen zonder artritis, had ongeveer 40% een artritis volgens de reumatoloog. Dit suggereert dat artritis met moeite wordt vastgesteld door de huisarts bij het lichamelijk onderzoek. Een fundamenteel probleem hiervoor is meest waarschijnlijk de lage incidentie van IA en RA in huisartsenpraktijken, wat leidt tot een gebrek aan expertise bij de huisartsen om artritis vast te stellen bij het lichamelijk onderzoek. Aangezien artritis echter een belangrijk item is van richtlijnen voor verwijzing en van de meeste verwijscriteria voor bestaande vroege artritis cohorten kan vroege verwijzing gehinderd worden. Het ontwikkelen van richtlijnen voor verwijzing die het vaststellen van artritis niet als vereiste hebben, kan wellicht vroege verwijzing van IA en RA verbeteren. Daarom hebben we in **hoofdstuk 3** een verwijsmodel ontwikkeld waarbij het niet nodig is om artritis vast te stellen bij het lichamelijk onderzoek. We vergeleken karakteristieken (demografisch, klinisch en zelfgerapporteerde klachten) van patiënten met IA zoals gediagnosticeerd door de reumatoloog met karakteristieken van patiënten zonder IA. We gebruikten statistische methodologie voor het ontwikkelen van klinische predictieregels om een verwijsmodel te maken wat niet meer karakteristieken gebruikt dan een tiende van het aantal events. Dit resulteerde in een model met een gewogen score van 0 tot 11. De volgende karakteristieken maakten deel uit van het model: geslacht, tangentiële drukpijn van de handen en voeten, een acuut begin van de klachten, klachtenduur tussen 3 en 6 maanden, afwezigheid van vermoeidheid en een aantal zelf gerapporteerde gewrichtsproblemen: bewegingsbeperking, pijnlijke, gezwollen, rode of warme gewrichten. De score waarboven patiënten verwezen zouden moeten worden was 6. Het model toonde veelbelovende resultaten met een AUC van 0.80 (95% CI: 0.76-0.85) en een aangepaste AUC van 0.77 (95% CI: 0.72-0.82) na interne validatie door middel van bootstrap. Ondanks de eenvoud heeft het model veelbelovende resultaten laten zien bij interne validatie, wat zou betekenen dat het een goede optie lijkt voor gebruik in de huisartsenpraktijk. Maar natuurlijk is externe validatie noodzakelijk.

Deel 2 – Uitdagingen voor vroege herkenning in de tweede lijn

Deel 2 van dit proefschrift is gericht op de uitdagingen van vroeg diagnostiek in de tweede lijn. Twee thema's zijn bestudeerd: 1) herkennen van IA onder artralgie patiënten, en 2) vroegtijdige herkenning van RA.

Herkenning van IA onder artralgie patiënten

Veel patiënten presenteren zich met artralgie zonder artritis bij het eerste bezoek aan de reumatoloog. De meeste van deze patiënten met artralgie zullen geen IA of RA ontwikkelen, maar sommigen kunnen wel later wel degelijk IA ontwikkelen. Als deze patiënten geïdentificeerd en gemonitord kunnen worden, hebben ze een kans op vroege behandeling.

In **hoofdstuk 4** hebben we de incidentie van IA onder artralgie patiënten uit de REACH vastgesteld. We hebben gezien dat 15% van de artralgie patiënten uit de REACH IA ontwikkelden. Factoren die geassocieerd waren met deze ontwikkeling waren ACPA, reumafactor en de bezinking. ACPA had de sterkste associatie (OR 6.31, 95% CI: 3.07-13.00). In de subpopulatie van ACPA en reumafactor negatieve patiënten was de incidentie 12%. De bezinking was het enige item wat hiermee geassocieerd was in deze subpopulatie.

De ACPA en reumafactor positieve artralgie patiënten zijn nader bestudeerd in **hoofdstuk 5**. Een eerder ontwikkeld predictiemodel om patiënten met een risico op IA te identificeren werd gevalideerd in dit hoofdstuk. Er werd gebruik gemaakt van 77 ACPA en reumafactor positieve artralgie patiënten uit de REACH en 77 ACPA en reumafactor positieve artralgie patiënten uit het AMC. Discriminatie was redelijk met een AUC van 0.74 (95% CI: 0.72-0.76), wat lager was dan de AUC van 0.81 (95% CI: 0.76 to 0.87) gepresenteerd in de oorspronkelijke studie. Het vergelijken van voorspelde waarden met geobserveerde waarden op basis van calibratie plots toonde wat onderschatting van het voorspelde risico in patiënten met een hoger risico. Dit zou in de praktijk betekenen dat het model het risico kan onderschatten bij patiënten met een risico groter dan 60%. Sensitiviteit en specificiteit waren optimaal bij een score van 7 met een sensitiviteit van 0.65 (95% CI: 0.51-0.79) en een specificiteit van 0.71 (95% CI: 0.61-0.80).

De gepresenteerde data over artralgie patiënten suggereert dat het mogelijk zou moeten zijn om patiënten te identificeren voor het actief monitoren door reumatologen zodat incidente gevallen van IA kunnen worden gedetecteerd. Dit zou deze patiënten een kans geven op vroege behandeling en een optimale uitkomst.

Vroeg diagnostiek van RA onder patiënten met IA

De 1987 ACR classificatie criteria zijn gebruikt voor diagnostiek ondanks dat ze ontwikkeld zijn om een selectie te maken van homogene patiënten voor klinische studies. Ze zijn samengesteld uit karakteristieken die kenmerkend zijn voor langbestaande ziekte, zoals noduli en erosies. Dit beperkt hun gebruik bij vroege ziekte. Om deze reden zijn nieuwe classificatie criteria geïntroduceerd in 2010.

De ontwikkeling van deze criteria was het resultaat van een trend richting vroeg herkenning van RA wat al eerder geleid had tot de ontwikkeling van twee predictiemodellen uit het Leiden vroege artritis cohort.

Beide bestaande modellen uit het Leiden vroege artritis cohort en de 2010 ACR/EULAR criteria werden gevalideerd in **hoofdstuk 7** om mogelijke diagnostische prestaties te evalueren. Discriminatie was goed voor alle modellen met AUCs boven de 0.79 voor elk model. Het gebruik van de afkapwaarden zoals voorgesteld door de auteurs van de modellen leidde tot een sensitiviteit van 0.6 en 0.8 voor het Visser model en de 2010 ACR/EULAR criteria. Het model van van der Helm toonde een sensitiviteit van 0.1 wat zou leiden tot fout negatieven waardoor de start van behandeling vertraagd kan worden. Door een hoge specificiteit was de AUC vergelijkbaar met de andere modellen.

Ondanks een goede prestatie van de 2010 ACR/EULAR criteria, kan de gekozen afkapwaarde leiden tot misclassificatie van patiënten als niet-RA. Om de risicostratificatie van gemisclassificeerde patiënten te verbeteren zouden verschillende strategieën overwogen kunnen worden zoals het verbeteren van beeldvorming of het aanpassen van de afkapwaarde. Aangezien conventionele beeldvorming ongevoelig is voor vroege verandering van bot en kraakbeen kan overwogen worden om andere beeldvormende technieken te gebruiken om deze veranderingen in beeld te brengen. Periarticulaire osteoporose is 1 van deze vroege veranderingen van het bot en dit zou gemeten kunnen worden met behulp van Dual X-ray Absorptiometry (DEXA). We hebben een accurate techniek ontwikkeld om periarticulaire osteoporose te meten in **hoofdstuk 6**. Hiervoor hebben we gezonde personen gebruikt. Vervolgens hebben we de validiteit getest om RA te diagnosticeren. Vroege IA patiënten, RA patiënten werden gemeten en de waardes werden vergeleken met gezonde controles die gematcht zijn op leeftijd, geslacht en de status van de menopause. Echter, overlappende waarden tussen patiënten met RA, IA en gezonde controles verhinderen het diagnostisch gebruik van periarticulaire osteoporose gemeten middels DEXA. Er zijn geen andere beeldvormende technieken bestudeerd in het kader van dit proefschrift. Maar we hebben wel een andere manier getest om de sensitiviteit te verhogen. We hebben het gebruik van een andere afkapwaarde getest in **hoofdstuk 8**. Sensitiviteit en specificiteit is berekend voor alle mogelijke afkapwaarden voor patiënten van het REACH cohort. Bij een afkapwaarde van 5 werd gezien dat de specificiteit 14% hoger was dan bij de door de auteurs voorgestelde afkapwaarde, wat een toename van 14% betekent van patiënten die geïdentificeerd kunnen worden met RA. Aangezien de specificiteit daalt met 8%, gaat dit ten koste van 8% meer patiënten die ten onrechte gediagnosticeerd worden met RA. Het voordeel van deze aanpassing is dat er geen additionele kosten aan verbonden zijn.

In **hoofdstuk 9** zijn alle resultaten samengevat en bediscussieerd rekening houdend met methodologische overwegingen, de huidige literatuur en implicaties voor de dagelijkse praktijk en toekomstig onderzoek.

Addendum

About the author

Celina Alves was born on the 30th of july in 1980 in Rotterdam. She grew up in Vlaardingen where she graduated in 1998 at the Groen van Prinsterer Lyceum. After a brief period at the Vrije Universiteit Medisch Centrum she transferred to the Erasmus MC where she graduated in medicine in 2002. Instead of starting her internships, she spent 2 years working as a datamanager in the Daniel den Hoed Clinic in Rotterdam. In 2004 she started her internships which she completed at the department of Rheumatology in 2006. Work on this thesis started in 2006 under the guidance of J.M.W. Hazes and J.J. Luime. Between 2006 and 2010 she obtained her degree in the Master of Science program Clinical Epidemiology by the NIHES (Netherlands Institute for HEalth Sciences). In 2010 she started her residency Internal Medicine in the Erasmus MC and the Sint Franciscus Gasthuis. Currently, she is working as a fellow in Rheumatology in the Sint Franciscus Gasthuis and she will continue her fellowship in the Erasmus MC.

PhD Portfolio

Summary of PhD training and teaching

Name PhD student: drs. C. Alves	PhD period: 2006 - 2014
Erasmus MC Department: Rheumatology	Promotor(s): Prof. Dr. J.M.W. Hazes
Research School: NIHES	Supervisor: Dr. J.J. Luime

1. PhD training

	Year
General courses	
- Biomedical English Writing and Communication	2009
- Statistics	NIHES
- Methodology	NIHES
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek'	2010
- Teach the teacher	2013
Specific courses (e.g. Research school, Medical Training)	
- NIHES master of science in clinical epidemiology	2007-2010
Seminars and workshops	
- Department Journal Club (attendance & presentations)	2006-2010
- ACR/EULAR joint task force meeting on new criteria	2009
- Meeting on "bone destruction in RA"	2008
Presentations (orals)	
- NVR najaarsdagen	2010
- tREACH seminar: 'the future of RA'	2010
- EULAR, Annual European Congress of Rheumatology	2010
- ACR/ARHP Annual Meeting	2012
(Inter)national conferences	
- EULAR, Annual European Congress of Rheumatology	2008 & 2010
- NVR najaarsdagen	2006-2009
- NHG wetenschapsdag 2008	2008
- ACR/ARHP Annual Meeting	2012
Other	
- Managing logistics of cohort	2007-2010

2. Teaching

	Year
Lecturing	
- Symposium on rheumatology for GPs	2007
- Rheumatology evening for GPs	2008
- Farmacotherapeutic education for GPs	2008-2009
Tutoring and supervising	
- Tutoring first year students	2007
- Supervising master thesis	2009 - 2010

3. Additional Publications

Kuijper TM, Luime JJ, Alves C, et al.Quality of life and health care use in patients with arthralgias without synovitis compared with patients diagnosed with early rheumatoid arthritis: data from an early arthritis cohort. *Published in Arthritis Care Res in 2014*.

Tilanus-Linthorst MM, Bartels KC, Alves C, et al.Selection bias influences reported contralateral breast cancer incidence and survival in high risk non-BRCA1/2 patients. *Published in Breast Cancer Res Treat in 2006.*

Tilanus-Linthorst MM, Alves C, Seynaeve C, et al. Contralateral recurrence and prognostic factors in familial non-BRCA1/2-associated breast cancer. *Published in Br J Surg. in 2006*.

Dankwoord

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