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EXTENDED REPORT

The incidence of rheumatoid arthritis in the UK: comparisons using the 2010 ACR/EULAR classification criteria and the 1987 ACR classification criteria. Results from the Norfolk Arthritis Register

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ABSTRACT

Objectives The development of new classification criteria for rheumatoid arthritis (RA) calls for a re-estimation of RA incidence rates. The objectives of this study were to estimate the age and sex-specific incidence rates (IR) of RA in Norfolk, England using the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism criteria, and to compare those with IRs estimated using the 1987 ACR criteria.

Setting The Norfolk Arthritis Register (NOAR), a large primary care inception cohort of patients with inflammatory oligo- and polyarthritis (IP) aged ≥ 16 .

Methods All patients notified to NOAR from 1990-5 with symptom onset in 1990 were included. The former Norwich Health Authority population was the denominator. Age and sex specific IRs using 1987 and 2010 classification criteria were calculated at baseline visit, annually for the first 3 years and at 5 years.

Results 260 patients were notified to NOAR with symptom onset in 1990 and without an alternative diagnosis. IRs applying the 2010 criteria at baseline were 54/100 000 for women and 25/100 000 for men. Age and sex-specific IRs using the 2010 classification criteria at baseline were similar to cumulative IRs applying the 1987 criteria up to 5 years. However, some patients only ever satisfied one set of criteria and a proportion of IA patients (20%) did not satisfy either criteria set over 5 years.

Conclusions The 2010 criteria classify similar numbers of patients as having RA at baseline, as the 1987 criteria would have taken up to 5 years to identify.

Rheumatism (EULAR) classification criteria for RA⁵ aim to have improved sensitivity compared with the 1987 criteria. In particular, the 2010 criteria were designed to better identify RA in patients presenting soon after the development of signs and symptoms of the disease.

The developers of the new criteria describe them as 'defining a new paradigm of RA'. If this is the case, previous estimates of disease incidence and prevalence may no longer be accurate. Measuring prevalence in a relapsing remitting disease, or disease in which signs and symptoms resolve with treatment such as RA, presents additional challenges, as patients on treatment may be completely asymptomatic and have no signs of disease; therefore may be missed by population surveys. Measuring incidence requires an inception cohort with complete capture of all new cases of disease within a stable, defined background population. To date, no studies have estimated incidence of RA using the 2010 criteria. The objectives of this study were (i) to estimate age and sex-specific incidence of RA using the 2010 criteria in Norfolk, UK and (ii) to compare these incidence rates (IR) with those using the previous criteria set, at initial presentation and cumulatively over 5 years.

PATIENTS AND METHODS

Setting

The Norfolk Arthritis register (NOAR) is a primary care inception cohort of patients aged ≥ 16 years presenting with ≥ 2 swollen joints for at least 4 weeks to either primary or secondary care within the former Norwich Health Authority. A detailed description of NOAR is available in previous publications.⁶ Briefly, patients undergo standardised assessment by a research nurse including details of symptom onset, 51 swollen and tender joint counts and examination for nodules, as well as consent to medical records review. Assessments (including joint counts and examination for nodules) are repeated annually for the first 3 years and at 5 years. Blood is taken at baseline and after 5 years for C reactive protein (CRP) and rheumatoid factor (RF) (latex test) and the remaining sera stored frozen; this was subsequently used to measure anti-citrullinated protein antibody status (ACPA) (Axis-Shield Diastat Anti-CCP kit, Dundee,

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, erosive inflammatory arthritis thought to affect approximately 1% of the UK adult population.¹ Recently it has been shown that aggressive early treatment can prevent much of the long term damage associated with the RA.² The 1987 American College of Rheumatology (ACR) classification criteria, widely used as entry criteria to clinical trials and observational studies, were developed in a cohort of patients with established, longstanding disease³ and are known to perform poorly in patients presenting with recent onset inflammatory arthritis,⁴ who may benefit most from early intensive treatment. The 2010 ACR/European League Against

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Scotland). Patients included in this current analysis were all those who had symptom onset of joint pain or swelling between January and December 1990, and were notified to NOAR within 5 years of symptom onset. This time period was selected as we can only be reasonably sure that all new cases of inflammatory oligo- and polyarthritis (IP) presenting to primary care were identified in 1990–1994 and we have previously reported on the incidence using the 1987 criteria for patients with a symptom onset in 1990.^{6,7} It should be noted that a group of patients from NOAR were used in the development of the 2010 criteria.⁵ However, those patients were recruited since 2000 and none of the patients included in the present study formed part of the criteria development cohort.

Application of classification criteria

For the 2010 criteria, joint counts and duration of symptoms were obtained from the nurse assessments and weighted scores assigned as detailed in the criteria (figure 1). In order to obtain as complete a dataset as possible, the medical records of those patients included in this analysis who did not provide a blood sample were searched to identify acute phase reactant (CRP or erythrocyte sedimentation rate (ESR)) and RF results taken near to the time of symptom onset. CRP and ESR were considered elevated if >5 mg/l and >10 mm/h respectively, according to local laboratory reference ranges. The 2010 criteria divide values of RF and ACPA into the following groups for scoring: negative: defined as $\leq$ upper limit of normal (ULN) for the laboratory and assay; low positive: $>ULN$ but ≤ 3 times ULN; and high positive: >3 times ULN. In this study these cut offs were 40 and 120 International Units (IU) respectively for RF; for ACPA they were 5 and 15 IU respectively.

The 1987 criteria exist in two formats: list (figure 1) and tree.³ The list format includes radiographic erosions, which can be substituted with clinical data in the tree format. At baseline assessment, radiographs were not taken, thus the tree format was applied; at 5 years all patients underwent radiographic examination of hands and feet and patients were said to have met the 1987 criteria if they satisfied the tree or list format.

For both criteria sets, if data were missing on any variables, total scores were calculated with the missing variable value taken as zero, and patients said to have met the criteria if they reached the defined cut-offs: $\geq 6/10$ for the 2010 criteria and $\geq 4/7$ for the 1987 criteria.

Incidence rates

The denominator population was provided by the former Norfolk Health Service Authority.⁶ Both criteria sets were applied to calculate age and sex-specific IRs at the baseline assessment. Using the 2010 criteria, 5 year cumulative incidence was estimated by taking the highest score for each parameter (joint count, serology, acute phase reactants and symptom duration) at any assessment over the 5 years follow up period. For the 1987 criteria, 5 years cumulative incidence was estimated in the following manner: if a patient satisfied a particular criterion at an individual assessment, it was then carried forward to all future assessments. CIs around the IRs were calculated using the Poisson distribution.

NOAR is approved by the Norwich Local Research Ethics Committee and all patients gave written consent. All data were analysed using STATA V.10 software package (Stata, College Station, Texas, USA).

RESULTS

A total of 283 patients were registered with NOAR who had symptom onset in 1990. Of these, 23 patients were diagnosed with other rheumatological disorders by their treating rheumatologist and were therefore excluded. Table 1 shows baseline demographic data of the cohort and the proportion of missing data. Thirty-six patients declined to provide a blood sample at baseline. Despite medical record review, 31 of these patients had no result for acute phase reactants and 12 patients had no autoantibody results at baseline. Five patients continued to decline blood sampling throughout follow up and therefore had no results available for the acute phase reactant or either autoantibody parameters. After 5 years, 25 patients had died, 22 patients declined follow up after baseline assessment and 16 patients were lost to follow up, thus a total of 197 patients remained under active follow up. For the cumulative analysis, patients who did not complete 5 years follow up were classified cumulatively up to their last assessment.

The overall IR when applying the 2010 criteria at baseline was 40/100 000; 54/100 000 for women and 25/100 000 for men. These rates were higher than when applying the 1987 criteria at baseline (32/100 000 overall, 45/100 000 for women and 18/100 000 for men). Age and sex-specific IRs using the 2010 classification criteria at baseline showed marked similarities to cumulative IRs applying the 1987 criteria up to 5 years (table 2). In women the peak age of incidence was younger than in men for both criteria sets, with highest rates between ages 45–74. In men incidence appeared to increase with age with highest rates in men over 65 years old.

Applying the 2010 criteria cumulatively over 5 years follow up gave an estimated IR of 48/100 000; for the 1987 criteria this was 44/100 000. A further 34 patients satisfied the 2010 criteria when applied cumulatively over 5 years; applying the 1987 criteria cumulatively for 5 years classified 49 additional patients as RA. Results applying both criteria sets cumulatively converged after approximately 3 years follow up (figure 2 and table 3); nevertheless there remained some discordance between the criteria (table 4). After 5 years follow up, 50 (19%) patients satisfied neither criteria set, cumulatively or cross-sectionally. All five patients who had no blood results throughout the follow up period met at least one criteria set at baseline.

DISCUSSION

The 2010 ACR/EULAR classification criteria for RA have provided a new definition for the disease entity 'RA'. This is the first study to estimate the incidence of RA using the 2010 criteria. We have shown, in a cohort of patients with early IP, that the incidence of RA according to the 2010 criteria is higher at baseline assessment than the incidence of RA according to the 1987 criteria. The 2010 criteria appear to identify at baseline similar rates of RA as the 1987 criteria identify cumulatively over 5 years. We have shown previously that cumulative application of the 1987 criteria over 5 years increases incidence estimates by up to 93%.⁷ However, this requires long term follow up of all patients presenting with undifferentiated inflammatory arthritis. Today, with improved treatment strategies, some patients who are given a clinical diagnosis of RA by their treating physicians may never satisfy them. Our results show that application of the 2010 criteria in early disease may therefore negate the need for such long term follow up to confirm classification, and may in part address concerns that some patients, whose disease is suppressed by appropriate treatment, may be inappropriately classified as not having RA.

Criterion	Definition
A patient is classified as RA if 4/7 criteria are satisfied. Criteria 1-4 must have been present for ≥6 weeks	
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least an hour before maximal improvement
2. Arthritis of ≥3 joints areas	≥3 joints areas simultaneously have had synovitis observed by a physician
3. Arthritis of hand joints	At least 1 area swollen in a wrist, MCP or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas on both sides of the body
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, extensor surfaces or juxta-articular regions
6. Serum rheumatoid factor (RF)	Positive RF
7. Radiographic changes	Radiographic changes typical of RA in posteroanterior hand and wrist radiographs

1987 ACR Classification criteria for RA[3]

Target population: Patients who (i) have at least one joint with clinical synovitis, and (ii) the synovitis not better explained by another disease		Score
Add score of categories A-D, score of ≥6/10 needed to classify patient as having definite RA		
A. Joint involvement (tender/swollen)		
1 large joint		0
2-10 large joints		1
1-3 small joints (with or without involvement of large joints)		2
4-10 small joints (with or without involvement of large joints)		3
>10 joints (at least 1 small joint)		5
B. Serology		
Negative RF /ACPA		0
Low-positive RF/low positive ACPA		2
High positive RF/high-positive ACPA		3
C. Acute phase reactants		
Normal CRP&ESR		0
Abnormal CRP/ESR		1
D. Duration of symptoms		
<6 weeks		0
≥6 weeks		1

2010 ACR/EULAR Classification criteria for RA[5]

Figure 1 Classification criteria for RA.

Incidence of RA has been estimated in a variety of populations, with considerable variation in the results.⁸ In the USA, the incidence of RA in Olmsted County, Minnesota has been tracked since 1955 using the Rochester Epidemiology Project

medical record linkage system.⁹ They, and others, have shown a decline of the incidence of RA in the second half of the 20th century.^{10 11} Interestingly, this trend may have slowed or even reversed in the past 10 years and their latest published IR was 41/100 000 population,¹² which is higher than our estimate using the 1987 criteria. It will be interesting to assess whether these long term trends in incidence will continue given the re-definition of disease in the 2010 criteria. Another recent estimation of RA incidence based on the 1987 criteria was undertaken in Spain, where cases were identified from primary care during the establishment of a nationwide programme of early arthritis units.¹³ They estimated an IR of 8/100 000, significantly lower than ours applying the same criteria set. This may be due to the reported lower incidence of RA in Southern Europe compared to Northern Europe (8). Where inception cohorts are not available, other methods have been used to estimate incidence. In the UK, a combination of diagnostic codes and disease modifying drug prescriptions recorded within the General Practice Research Database (GPRD)¹⁴ were used to identify new cases; in Finland insurance claim forms have been used.¹¹ In both cases, data were collected retrospectively, and, in particular with the GPRD, the definition of incident RA is vulnerable to misclassification.

Studies assessing the 2010 criteria to date have mainly focused on their sensitivity and specificity to predict surrogates of an RA diagnosis (for which there is no gold standard) such as initiation of disease modifying anti-rheumatic drug therapy,^{15 16} physician opinion¹⁷ and absence of drug free remission.¹⁸ These studies have shown that the 2010 criteria classify more patients as RA earlier in the disease course compared to the 1987 criteria, with a general improvement in sensitivity at the cost of specificity. Our findings support this hypothesis, that the 2010 criteria are better at classifying early RA; in addition we have demonstrated that this earlier classification identifies similar rates of disease. However, the lack of gold standard is also a limitation in our study, as without this it is not possible to measure true incidence.

This study highlights certain subgroups of patients who may be of particular interest for further investigation. The first is those patients who only met one criteria set over the 5 years

Table 1 Baseline demographics and criteria variables

Demographic	Frequency	Missing n (%)
Age at symptom onset (mean (SD))	54 (16.2)	0
Female (n (%))	173 (69)	0
Symptom duration in weeks (median (IQR))	29.6 (4.3–71.9)	0
RF low positive (n (%))	25 (11)	28 (11)†
High positive (n (%))	47 (20)	
ACPA low positive (n (%))	6 (3)	77 (30)†
High positive (n (%))	38 (20)	
Joint involvement* (n (%))		0
1 large joint	9 (3)	
2–10 large joints	9 (3)	
1–3 small joints	41 (16)	
4–10 small joints	52 (20)	
>10 joints	149 (57)	
Acute phase reactant positive (n (%))	120 (52)	27 (10)
CRP	116 (48)	
ESR	9 (64)	
CRP (mean (std dev))	19 (35)	
ESR (mean (std dev))	30 (34)	
Morning stiffness ≥60 min (n (%))	172 (66)	0
Arthritis of ≥3 joints areas (n (%))	172 (66)	0
Arthritis of hand joints (n (%))	215 (83)	0
Symmetric arthritis (n (%))	183 (70)	0
Rheumatoid nodules (n (%))	19 (7)	0

*Large joints were defined as shoulders, elbows, hips, knees and ankles. Small joints are defined as metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints and wrists. Distal interphalangeal joints, first carpometacarpal joints and first metatarsophalangeal joints were excluded as per the 2012 criteria.⁵

†Missing data quoted are for individual autoantibodies. 8 (2%) patients had no results for ACPA or RF.

ACPA, anti-citrullinated protein antibody; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

Table 2 Age and sex specific incidence rates (IR/100 000 population)

Age band	No. of patients with inflammatory oligo- and polyarthritis	Female patients		Male patients	
		2010 criteria at baseline IR (95% CI)	1987 criteria cumulative to 5 years follow up IR (95% CI)	2010 criteria at baseline IR (95% CI)	1987 criteria cumulative to 5 years follow up IR (95% CI)
15–24	17	18.6 (6.8 to 40.6)	15.5 (5.0 to 36.3)	0 (0 to 11.1)	6 (0.7 to 21.7)
25–34	23	20.3 (8.2 to 41.8)	31.9 (15.9 to 57.0)	5.6 (0.7 to 20.3)	8.4 (1.7 to 24.6)
35–44	34	56.6 (34.1 to 88.4)	56.6 (34.1 to 88.4)	12.1 (3.3 to 30.9)	12.1 (3.3 to 30.9)
45–54	53	85.6 (56.4 to 124.6)	98.3 (66.8 to 139.5)	34.5 (17.2 to 61.7)	31.4 (15.0 to 57.7)
55–64	58	91.8 (59.4 to 135.5)	91.8 (59.4 to 135.5)	42.1 (21.0 to 75.3)	42.1 (21.0 to 75.3)
65–74	53	87.1 (55.8 to 129.6)	94.4 (61.7 to 138.3)	58.3 (31.9 to 97.8)	66.6 (38.1 to 108.2)
75+	22	26.1 (10.5 to 53.7)	29.8 (12.9 to 58.7)	44.3 (17.8 to 91.3)	57.0 (26.1 to 108.1)
Total	260	53.9 (44.5 to 64.7)	58.5 (48.7 to 69.8)	24.5 (18.1 to 32.4)	27.5 (20.7 to 35.8)

follow up period. The characteristics of these patients reflect the criteria themselves: patients satisfying only the 1987 criteria were more likely to have prolonged morning joint stiffness, they also had more symmetrical and more hand joint involvement. By contrast, patients satisfying only the 2010 criteria had greater number of joints involved at each assessment (reflecting the inclusion of tender as well as swollen joints). The most notable difference is seen in the frequency of autoantibodies. The majority of patients in our cohort who never satisfied the 2010 criteria but did satisfy the 1987 criteria were autoantibody negative; this difference was most marked at baseline assessment. This pattern has been noted in other cohorts,^{19 20} and it has been postulated that the two criteria sets may be describing different clinical entities.²¹ However, the striking similarity in IRs over time in our patients argues against this. It may be that the two criteria sets represent different aspects of the same disease construct; the 2010 criteria describe an acute inflammatory arthritis, whereas the 1987 criteria describe the long term damage that occurs as a consequence. Another subgroup of interest is those patients who never satisfy either criteria set. For patients remaining in this

study 5 years after symptom onset, this group comprised 50 patients (19%), which is a substantial proportion. There were missing data in our cohort, particularly relating to serological markers, and this may have led to some patients being misclassified as non-RA. However, none of the patients who could not be classified by either criteria set over 5 years had missing data on all serological variables at all time points. Investigating the long term outcomes of the patients who satisfy neither criteria set will be important to assess the validity of the 2010 criteria.

In the publication describing the development of the 2010 criteria,⁵ and in subsequent editorials²² the authors suggest they may be used in clinical practice to allow access to disease modifying anti-rheumatic drug or biologic therapy. Although we have shown that these criteria classify more patients early in the disease course than the previous criteria set (which were never used in this context), our results suggest they are not sufficiently sensitive for this purpose. In particular, the fact that some patients fulfil the previous criteria set without fulfilling the new criteria, even after 5 years follow up, indicate caution should be taken considering this application. Further work is needed to elucidate the long term outcomes of patients not fulfilling the new criteria to answer this question. If these are universally good for all patients not fulfilling the criteria, their use as a gateway to treatment may be appropriate. There are a number of strengths in the present study due to unique features of NOAR in the UK: Norfolk has a stable population with little migration, there is a balanced mix of rural and urban populations (thus is representative of both) and a central referral system for musculoskeletal patients to a single secondary care provider, Norwich and Norfolk University Hospital. Significant efforts were made to ensure all patients with IP newly presenting to primary care were reported to NOAR

Figure 2 Cumulative incidence of RA in patients satisfying both criteria sets after 5 years (n=170).**Table 3** Patients satisfying rheumatoid arthritis criteria cumulatively over time

	Satisfy 1987 criteria cumulatively	Satisfy 2010 criteria cumulatively	Satisfy both criteria sets cumulatively	Satisfy 1987 criteria cumulatively if satisfy both by 5 years	Satisfy 2010 criteria cumulatively if satisfy both by 5 years
Baseline	131/260	166/260	119/260	125/170	145/170
1 year	163/260	186/260	150/260	154/170	161/170
2 years	174/260	193/260	159/260	164/170	164/170
3 years	177/260	197/260	165/260	167/170	168/170
5 years	180/260	200/260	170/260	170/170	170/170

Table 4 Number of patients satisfying each criteria set after 5 years follow up

	Patients satisfying 1987 criteria cumulatively n (%)	Patients not satisfying 1987 criteria cumulatively n (%)	Total
Patients satisfying 2010 criteria cumulatively	170 (65)	30 (12)	200
Patients not satisfying 2010 criteria cumulatively	10 (4)	50 (19)	60
Total	180	80	260

when it was first established in 1989, with visits to GP practices, advertising and a small incentive. We therefore selected the year 1990 to estimate incidence in this study as the year with near complete capture of all patients presenting with early IP. Nevertheless, the IRs reported here are likely to be an underestimate for a number of reasons. Some patients only had RF or ACPA measured; a high positive result in the other auto-antibody may have increased the number of patients classified as RA. However, the 2010 criteria only require testing of either RF or ACPA, therefore our data represent a valid estimate of incidence. NOAR was established when the 1987 criteria were the standard for classification, and elements of its design may make classification by the 1987 criteria easier than by the 2010 criteria, potentially reducing the IRs using the 2010 criteria. This highlights difficulties that occur when applying criteria retrospectively to an historic cohort. In addition, there may have been cases which were not captured, including patients who did not seek healthcare advice at the time of symptom onset. To allow for this delay and to obtain as true an estimate of incidence in that year as possible, the age and sex-specific IRs reported at baseline included patients who had presented to NOAR up to 5 years after symptom onset. However, this meant that a small number of patients had been symptomatic of their disease for a number of years at the time of initial assessment. If IRs were calculated based on initial assessments of only those patients who presented within 2 years of symptom onset, the overall IR using the 2010 criteria was 35/100 000 population; for 1987 criteria it was 27/100 000 at baseline presentation but increased to 36/100 000 cumulatively 5 years after symptom onset.

A further limitation relates to erosive disease. The 2010 criteria include an amendment which states that any patient with radiological evidence of erosion typical of RA should automatically be classified as having RA, without the need to fulfil any other aspect of the criteria. As radiographs were not performed at baseline in this cohort, and because there is no clear definition of 'typical RA erosion', this was not applied in the present analysis. x-Rays were performed on all patients after 5 years follow up; if the presence of any erosion (although not specifically a 'typical RA' erosion) was applied at that point, four further patients (three women and one man) could be classified as having RA according to the 2010 criteria.

In conclusion, we have reported the first IR estimates of RA applying the 2010 ACR/EULAR classification criteria. We have shown that the incidence of RA, as estimated by the 2010 classification criteria at baseline, is very similar to the estimates using the 1987 criteria cumulatively over 5 years. These results indicate that the 2010 criteria may identify RA patients earlier in the disease course and will be important in order to plan

timely, cost-effective and efficacious management of patients presenting with inflammatory arthritis.

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