Rheumatoid arthritis is not a single disease

Sirs,

The 2010 ACR classification criteria for rheumatoid arthritis (RA) (1) consider the number and size of the affected joints, symptom duration, acute phase reactants, and two seromarkers: rheumatoid factor (RF) and anti-citrullinated-peptide antibodies (ACPAs). For classification, one to three joints suffice, if either seromarker is present. If both are negative, more than ten joints are required. If typical erosions are detected on x-ray radiographs, RA classification is fulfilled, regardless of other criteria.

RF is also found in chronic inflammatory disease, like Sjögren's syndrome, and in elderly individuals (2), ACPAs are highly specific (2). Seroconversion, especially of ACPAs, is rare (3). The specificity of ACPA suggests that this marker is pathophysiologically relevant, the significance of isolated RF is unclear. The nomenclature concerning ACPA and RF is inconsistent. Some clinicians reserve the term 'seropositive' for RF-positive RA, whereas others, including us, use this term for RF- and/or ACPA-positive patients.

Some patients with idiopathic arthritis do not fulfil any defined disease criteria. This 'undifferentiated peripheral inflammatory arthritis' (UPIA) is poorly described, and is considered an exclusion diagnosis (4). UPIA patients are mostly seronegative (5). Seropositive UPIA patients more often develop RA and erosions (6). Some patients suffer from chronic arthritis without ever fulfilling RA criteria. No other predictive factors for UPIA are known.

Despite attempts to 'close the serological gap', *i.e.* to identify serological markers for seronegative RA (7), around 30% of patients classified as RA remain seronegative. A subgroup of seronegative RA presents as late-onset RA (LORA) which manifests in older patients and is often preceded by a polymyalgiform prodromic phase (6).

Several studies and analyses have found differences between seropositive and seronegative RA (spRA and snRA, respectively). The differences are modest, at times conflicting (8), and the studies involved are often inadequately powered to find significant differences. The clinical relevance of these findings is often disputable. It has been found that spRA patients develop more erosions (6), respond differently to biologic DMARDS (8), and, solely for these patients, smoking (9) appears to be a negative prognostic factor. The 'shared epitope' allele predisposes for spRA (9) only, and spRA and snRA also differ in genome-wide association studies (10), on conventional x-ray radiographs (11), and in power-Doppler sonography (PDS) (12). The prognostic value of seromarkers is limited: debilitating disease does occur in snRA (13).

Fig. 1. Incidence of RA in different age groups in Minnesota study (14).

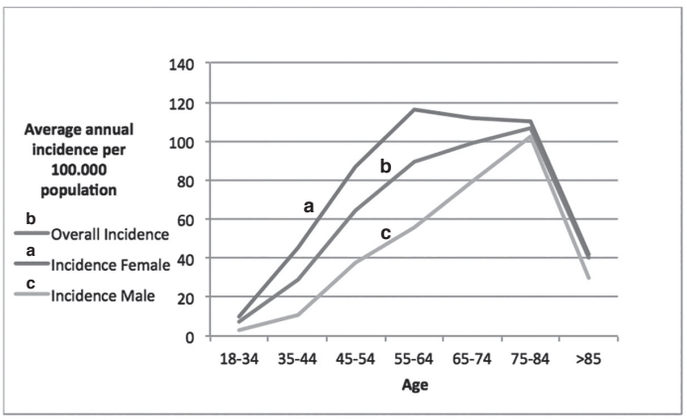
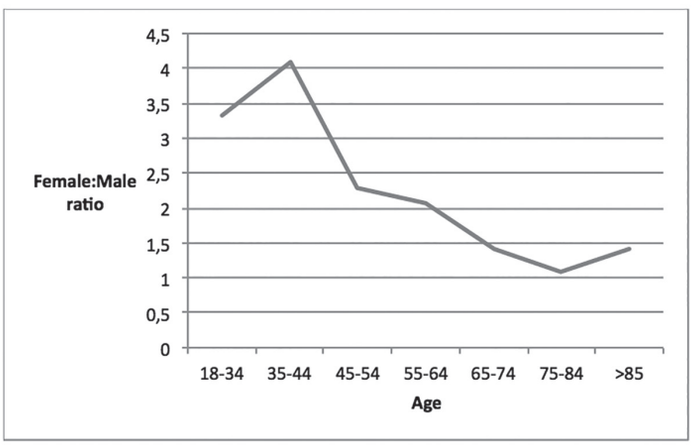


Fig. 2. Female:Male ratio of RA in different age groups in Minnesota study (own calculation).



Epidemiological data (14) show that RA predominantly affects females, and that the incidence increases with age (Fig. 1). The female:male ratio decreases with age, from >3:1 between 18 and 44 to <1.5:1 for patients of 65 and older (own calculation, Fig. 2). This could be because gender distribution is more balanced in LORA than in earlier-onset RA (15).

The current classification implicitly assumes that spRA and snRA are two forms of the same disease, with RF and ACPA being risk factors for a severe course.

This paradigm ignores chronic arthritis patients not fulfilling the RA criteria. It fails to predict disease severity in seronegative patients. Erosive disease is automatically classified as RA (1), erosions are the main hallmark of severity. Hence, the benign prognosis of UPIA is at least in part based on a circular argument. Also, when seropositive UPIA is more likely to fulfil the criteria for RA than seronegative, it is because seropositivity itself is a classification criterion.

Many ACPA-negative patients, including LORA, present with a uniform phenotype, characterised by symmetrical wrist arthritis, tendovaginitis of the wrist extensor and long biceps tendons, and subdeltoideal or subacromial bursitis. Unlike spRA, MCP and MTP joints are initially rarely affected. PDS oscillation amplitude is high (12). If untreated, the patients develop severe shoulder bursitis, arthritis of the shoulder and metacarpophalangeal joints and destruction of the carpal ossicles with hyperostosis of the ulnar styloid process. Erosions are less prominent than in ACPA-positive RA, even in severely damaged or luxated joints. Most, but not all patients are above 60 years of age. As expected in an elderly population, RF is occasionally present. Consequently, only some of these patients fulfil the RA criteria.

We suggest that these patients suffer from a disease distinct from RA, with ACPA, joint distribution, and x-ray, and power-Doppler findings being differentiating traits. This would explain the varying gender distribution in different

age groups, and the genetic and clinical differences described above. This entity likely encompasses some patients currently classified as UPIA.

To test this hypothesis, it would be necessary to investigate patients with this phenotype specifically, disregarding RA classification. These findings should then be compared to other seronegative phenotypes and, in particular, to ACPA-positive RA. The failure of previous studies to produce consistent results is likely due to RF-positive, ACPA-negative patients being included in the 'seropositive' collective, confounding findings; in our hypothesis, only ACPA status is relevant.

At present, our hypothesis has no clinical implications. Current treatment guidelines (16) recognise RF/ACPA as poor prognostic factors, but do not differentiate them from others, such as poor initial DMARD response. Both spRA and snRA generally respond to the currently available therapeutic modalities, and any difference in efficacy is unlikely to be clinically relevant. Similar levels of response, however, are not a valid argument that spRA and snRA are the same disease; psoriatic arthritis is a different entity to RA, yet it still responds to TNF-alpha inhibition.

The potential consequences are considerable. Firstly, pathogenetical and pathophysiological insights depend on an adequate taxonomy. If spRA and snRA are indeed two different entities, the presence of both within an epidemiological survey or therapeutic study collective will confound results and possibly lead to inadequate sample size estimates and bias. Separating the two groups would prevent systematic errors and hence improve care. Secondly, improved classification criteria could reduce the number of patients classified as UPIA, and ensure initiation of therapy in these patients before any erosions (which would lead to RA classification) occur.

Finally, considering how lymphoma patients have benefitted from a more detailed taxonomy, with treatment regimes depending on the genetic and phenotypical profile of the individual patient, it is possible that all RA patients would profit from a more individualised approach, based on improved taxonomy.

Owing to the emphasis on RF and ACPA, seronegative arthritis has been somewhat neglected. Accepting that spRA and snRA are different diseases could help improving care for all RA patients, independent of serological status.

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References

1. ALETAHA D, NEOGI T, SILMAN AJ *et al.*: 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69: 1580-8.
2. GOODYEAR CS, TIGHE H, MCINNES IB: Rheumatoid Factors and Other Autoantibodies in Rheumatoid Arthritis. *In*: FIRESTEIN GS, BUDD, RC, HARRIS JR ED, MCINNES IB, RUDDY S, SERGENT JS (Eds.): Kelley's Textbook of Rheumatology, 8th Ed., Philadelphia 2009.
3. BARRA L, POPE J, BESSETTE L, HARAOUI B, BYKERK V: Lack of seroconversion of rheumatoid factor and anti-cyclic citrullinated peptide in patients with early inflammatory arthritis: a systematic literature review. *Rheumatology* (Oxford) 2011; 50: 311-6.
4. MACHADO P, CASTREJON I, KATCHAMART W *et al.*: Multinational evidence-based recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2011; 70: 15-24.
5. QUINN MA, GREEN MJ, MARZO-ORTEGA H *et al.*: Prognostic factors in a large cohort of patients with early undifferentiated inflammatory arthritis after application of a structured management protocol. *Arthritis Rheum* 2003; 48: 3039-45.
6. HARRIS JR ED, FIRESTEIN GS: Clinical Features of Rheumatoid Arthritis. *In*: FIRESTEIN GS, BUDD, RC, HARRIS JR ED, MCINNES IB, RUDDY S, SERGENT JS (Eds.): Kelley's Textbook of Rheumatology, 8th Ed., Philadelphia 2009.
7. TROUW LA, MAHLER M: Closing the serological gap: promising novel biomarkers for the early diagnosis of rheumatoid arthritis. *Autoimmun Rev* 2012; 12: 318-322.
8. MARTIN-MOLA E, BALSA A, GARCÍA-VICUNA R *et al.*: Anti-citrullinated peptide antibodies and their value for predicting responses to biologic agents: a review. *Rheumatol Int* 2016; 36: 1043-63.
9. SILMAN AJ: Rheumatoid Arthritis. *In*: SILMAN AJ, HOCHBERG MC (Eds.): Epidemiology of the Rheumatic Diseases. Oxford University Press, 2001: 31-71.
10. PADYUKOV L, SEIELSTAD M, ONG RT *et al.*: A genome-wide association study suggests contrasting associations in ACPA-positive versus ACPA-negative rheumatoid arthritis. *Ann Rheum Dis* 2011; 70: 259-65.
11. BURNS TM, CALIN A: The hand radiograph as a diagnostic discriminant between seropositive and seronegative 'rheumatoid arthritis': a controlled study. *Ann Rheum Dis* 1983; 42: 605-12.
12. GADEHOLT O, WECH T, SCHUH S *et al.*: Anti-CCP status determines the power Doppler oscillation pattern in rheumatoid arthritis: a prospective study. *Rheumatol Int* 2016; 36: 1671-5.
13. NIKIPHOROU E, SJÖWALL C, HANNONEN P, RANNIO T, SOKKA T: Long-term outcomes of destructive seronegative (rheumatoid) arthritis - description of four clinical cases. *BMC Musculoskelet Disord* 2016; 17: 246
14. DORAN MF, POND GR, CROWSON CS, O'FALLON WM, GABRIEL SE: Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. *Arthritis Rheum* 2002; 46: 625-31.
15. TAN TC, GAO X, THONG BY *et al.*: Comparison of elderly- and young-onset rheumatoid arthritis in an Asian cohort. *Int J Rheum Dis* 2016 May 2 [Epub ahead of print].
16. SMOLEN JS, LANDEWÉ R, BIJLSMA J *et al.*: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017 Mar 6 [Epub ahead of print].