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Autoantibodies are major predictors of arthritis development in patients with anti-citrullinated protein antibodies and musculoskeletal pain

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Objectives: Predictors of arthritis development are highly warranted among patients with anti-citrullinated protein antibodies (ACPAs) and musculoskeletal symptoms to optimize clinical management. We aimed to identify clinical and laboratory predictors of arthritis development, including biochemically assessed alcohol consumption, among ACPA-positive patients with musculoskeletal pain.
Method: 82 ACPA-positive individuals with musculoskeletal pain but no clinical arthritis were followed for a median of 72 months (interquartile range 57–81 months). We evaluated the prognostic value of baseline clinical and laboratory factors including smoking, symptom duration, age, gender, shared epitope, rheumatoid factor (RF), anti-carbamylated protein antibodies, ACPA levels, erythrocyte sedimentation rate, C-reactive protein levels, tender joint count, patient-reported general well-being, 28-joint Disease Activity Score, and alcohol consumption as measured by phosphatidyl ethanol (PEth) levels in whole blood.
Results: During follow-up, 48% developed at least one arthritis. Multivariable analysis revealed an increased risk of arthritis development with RF positivity [hazard ratio (HR) = 2.3, 95% confidence interval (CI) 1.1–4.8, p = 0.028] and higher ACPA levels (HR = 1.0, 95% CI 1.000–1.001, p = 0.002). High levels of RF (HR = 4.4, 95% CI 1.7–11) entailed the highest HR in this ACPA-positive population. Neither clinical characteristics nor alcohol consumption measured by PEth conferred significant prognostic value.
Conclusions: ACPA levels and concurrent presence of RF are independent predictors of arthritis development among ACPA-positive patients with musculoskeletal pain. The results are compatible with a dose–response relationship between RA-related autoantibodies and risk of arthritis development.

Rheumatoid arthritis (RA) is considered to have a preclinical phase where levels of circulating autoantibodies are increased, but without clinical signs of arthritis (1–3). Since early pharmacotherapy is advocated in RA, this period may enable a 'window of opportunity' for even earlier onset of therapy, with possible benefits regarding disease course and even prevention of disease (1, 3–5). Individuals with anti-citrullinated peptide antibodies (ACPAs) and musculoskeletal pain or arthralgia face an increased risk of developing RA, and may thus represent a category of patients where very early interventions could be beneficial (6, 7). In other rheumatic diseases, such as Sjögren's syndrome and systemic lupus erythematosus, the presence of ACPAs identifies patients prone to arthritis development (8, 9). However, as not all patients with ACPAs and arthralgia develop arthritis, prognostic factors identifying patients who may develop RA in the near future are highly warranted (2, 10, 11), and the risk of overtreatment must continuously be considered.

The 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for RA highlights the importance of autoantibodies for classification of RA, with ACPAs and rheumatoid factor (RF) being equally weighted (12). In many primary care settings, ACPA has replaced RF as the primary serological test when RA is suspected. In patients presenting with musculoskeletal symptoms or clinically suspect arthralgia, but no clinical synovitis, the prevalence of ACPA is 3–16% depending on the clinical context (13, 14), and these patients have become increasingly frequent in rheumatology clinics. In one study addressing the relative importance of the RA-related autoantibodies ACPA, RF, and anti-carbamylated antibodies (anti-CarPs), the occurrence of ACPAs appeared superior in predicting arthritis development (14). However, results

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from previous studies are diverging as to whether the actual circulating levels of ACPAs are predictive in such populations (6, 14–16). Furthermore, data are inconsistent concerning the additive effect of RF status among ACPA-positive cases (6, 14, 16) and whether anti-CarP antibodies independently predict arthritis development in at-risk populations (14, 17, 18). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are also part of the 2010 classification criteria and have been brought forward as predictors of arthritis development, with conflicting results (7, 16, 19, 20).

In addition to laboratory markers, certain lifestyle factors and clinical characteristics have been proposed to predict arthritis development among patients at risk of RA development (6, 7, 21). For instance, an inverse association between alcohol consumption and risk of arthritis development was reported from a Dutch at-risk cohort (22). This is in line with several prospective studies, where alcohol consumption was shown to reduce the risk of future RA development (23–25). However, this association was contradicted by others (26–28). A number of classical case–control studies, in which RA patients retrospectively estimated their alcohol consumption, revealed protective effects of alcohol consumption (29–31). Finally, ethanol in drinking water prevented destructive arthritis in a study on collagen-induced arthritis in mice (32).

Since studies diverge regarding healthcare settings, inclusion criteria, and follow-up periods, further studies are needed to validate and refine risk stratification of patients with autoantibodies and musculoskeletal symptoms. Data from the Nordic countries are still lacking in the literature, and biochemical assessments of alcohol consumption have not previously been explored in RA or at-risk populations. Thus, we aimed to identify clinical and laboratory predictors of arthritis development in a prospective cohort of ACPA-positive patients with musculoskeletal pain.

Method

Study population

This study was performed as part of the 'X-tra timely rheumatology follow-up' (TIRx) study, a prospective observational cohort enrolling 116 patients between 2010 and 2013 at the Rheumatology Clinic, Linköping University Hospital, Linköping, Sweden. Eligible patients were referred from primary care centres in Östergötland County Council (approximately 457 000 inhabitants) in south-eastern Sweden. In this region, as in most of Sweden, ACPA tests are important in the referral process, as general practitioners refer ACPA-positive patients with any musculoskeletal symptom to a rheumatology clinic, but not ACPA-negative patients with arthralgia if clinical signs of arthritis are absent. General practitioners throughout the region were informed about the study and encouraged to promptly refer ACPA-positive cases. Testing for RF was not generally recommended in primary care settings. The annual incidence of RA according to the ACR 1987 criteria for RA (32) was estimated as 24/100 000 in a nearby region (33).

The study protocol was approved by the Regional Ethics Committee in Linköping, Sweden (reference numbers M220-09, 2017/260-32, and Dnr 2019-02707). All subjects gave written informed consent to participate in the TIRx study.

Inclusion criteria in the TIRx study were a positive second generation anti-cyclic citrullinated peptide (anti-CCP) test in clinical routine, musculoskeletal pain of any sort and duration, and a maximum of one arthritis upon clinical examination. Exclusion criteria were fulfilment of ACR 1987 (34), previous inflammatory rheumatic disease, or corticosteroid treatment (oral or intra-articular) within 6 weeks prior to screening. The patients were followed by one out of four experienced rheumatologists participating in the study (AK, TS, JC, ÅR), who also treated the patients as was judged appropriate. Twelve out of the 116 patients enrolled in TIRx discontinued for various reasons [compliance (n = 4), moved (n = 1), never ACPA positive (n = 1), other comorbidities (n = 4)] (Figure 1), and 104 individuals were available for further analyses. Twenty-two out of the 104 patients (21%) had one clinical arthritis at inclusion, while 82 had none (79%). Baseline characteristics are shown in Table 1. The 82 patients without baseline arthritis were followed prospectively for the development of arthritis as judged by clinical examination by an experienced rheumatologist. Follow-up visits were scheduled after 3, 12, 24, and 36 months, and thereafter every second year. The patients were also encouraged to contact the rheumatology unit without delay in case of aggravated symptoms and, in doing so, they were offered an extra examination. Every visit included recording of the 28-joint Disease Activity Score (DAS28) (35) plus clinical examination of any symptomatic joint, a Swedish version of the Health Assessment Questionnaire (HAQ) (36), and routine laboratory tests. Follow-up included data until 1 September 2017, yielding a median follow-up time of 72 months [interquartile range (IQR) 57–81].

Antibody analyses

Anti-citrullinated protein antibodies. All patients had tested positive for ACPA at the accredited Clinical Immunology Laboratory at Linköping University Hospital, using second generation CCP as the antigen. Since the period between ACPA testing in clinical routine and enrolment varied between patients, we also chose to analyse baseline serum samples by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (EuroDiagnostica, Malmö, Sweden), with a cut-off of 25 arbitrary units (AU)/mL.

Rheumatoid factor. Agglutinating RF was measured at baseline by nephelometry at the accredited Laboratory of Clinical Chemistry, Linköping University Hospital, Sweden. The cut-off was 30 U/mL.

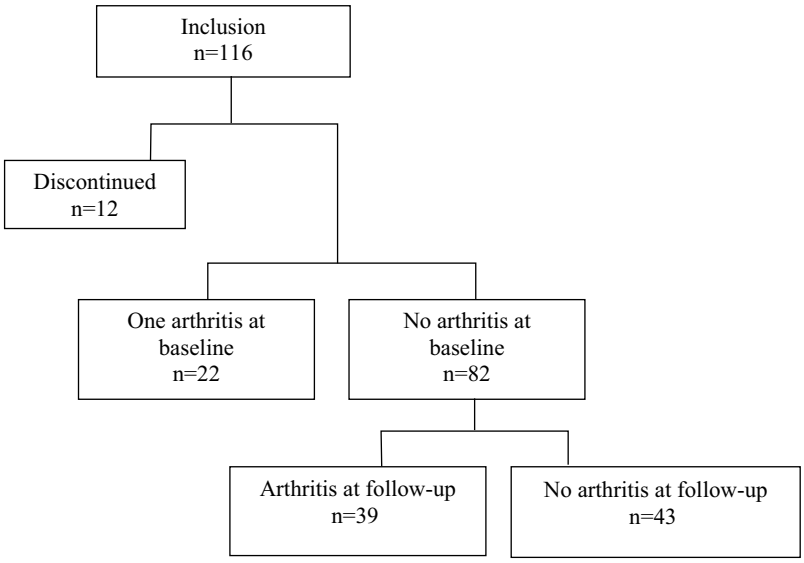

Figure 1. Flowchart of the TIRx study participants.

Anti-carbamylated protein antibodies

Anti-CarPs were analysed by ELISA in Leiden, the Netherlands, using carbamylated foetal calf serum (Ca-FCS) and non-modified FCS as antigens. The cut-off was 316 AU/mL, corresponding to the mean + 2 standard deviations (sd) among 98 healthy blood donors (49% women, mean age 52 years) from the same geographical area as the patients. As previously described, anti-CarP levels were obtained by subtraction of the reactivity to non-modified FCS from the reactivity to Ca-FCS (37).

Human leucocyte antigen (HLA) sequencing

HLA-DRB1 was genotyped by Sanger sequencing and the shared epitope (SE) was defined as *01, *0401, *0404, *0405, *0408, *0409, *0410, *0413, *0416, *0421, or*10, as previously described (38).

Phosphatidyl ethanol (PEth) analyses

PEth includes several phospholipids created in the presence of ethanol. In clinical routine, the subtype PEth 16:0/18:1 is most commonly measured, since it has the highest concentration in blood and strongly correlates with the total concentration of PEth (39). PEth 16:0/18:1 was analysed in baseline whole blood samples by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) (Acquity UPLC and Xevo TQ-S micro; Waters, Milford, MA, USA) at the accredited Clinical Pharmacology Laboratory in Linköping, Sweden. Chromatographic separation was performed on a BEH C18 2.1 × 50 mm, 1.7 µm (Waters) and BEH C18 VanGuard. The mobile phases were: A, 10 mM ammonium acetate/acetonitrile (80/20; v/v); B, methanol/acetonitrile (80/20; v/v). The flow rate was set to 0.6 mL/min and the total run time was 3 min. Extraction was performed by mixing 100 µL of blood and 200 µL of isopropanol. After vortexing, 800 µL of acetonitrile spiked with internal standards (phosphatidylethanol-D5) was added, vortexed, and centrifuged (5 min, 18 000 × *g*). The supernatant was loaded onto an Ostro plate (Waters) and filtered using a positive pressure manifold with nitrogen (Positive Pressure 96; Waters). The samples were eluted with 800 µL of acetonitrile/ultrapure water (80/20; v/v). Then, 10 µL of aliquot was injected into the UPLC system. The blood samples had been stored in EDTA tubes at −70°C prior to analysis. PEth 16:0/18:1 < 0.05 µmol/L was considered to represent no/low consumption, 0.05–0.3 µmol/L moderate consumption, and > 0.3 µmol/L high consumption (40).

Statistical analyses

Baseline characteristics were compared between subgroups using Mann–Whitney U tests, Fisher's exact test or Pearson chi-square depending on the variables measured. PEth levels were compared between subgroups of patients by Mann–Whitney U tests, and with Fisher's exact test when categorized. Univariable Cox regression analyses were used to test clinical and laboratory factors, including age, gender, smoking, PEth, symptom duration, global visual analogue scale (VAS), tender joint count, HAQ, DAS28, CRP levels, ESR, SE status, baseline ACPA levels, RF levels/status, anti-CarP levels/status, and antibody usage, versus clinical arthritis development. Antibodies were stratified into negative/low/high according to cut-off levels and 3 × cut-off levels. Variables with $p < 0.05$ in univariable analysis were included in the multivariable Cox regression analyses, with the exception of antibody strata and levels due to collinearity. Anti-CarP and triple positivity (i.e. testing positive for ACPA, RF, and anti-CarP) were added to the prespecified analytical plan owing to recently published data (41). The pattern of

Table 1. Baseline characteristics of the TIRx cohort.

	No baseline arthritis (n = 82)	One baseline arthritis (n = 22)	p
Age (years)	52 ± 14	52 ± 19	0.9
Female	66 (81)	17 (77)	0.8
RF	15 (15–41)	15 (15–98)	0.1
RF positive	24 (29)	10 (46)	0.2
Anti-CCP (AU/mL)	120 (33–347)	151 (29–630)	0.6
CRP	5 (5–5)	5 (5–15)	0.01
ESR	9 (5–16)*	12 (7–19)	0.3
Shared epitope carrier	52 (63)*	14 (64)	1.0
Current smoker	13 (16)	5 (23)	
Former smoker	26 (32)	3 (14)	
Symptom duration			0.5
0–6 months	15 (18)	6 (27)	
6–18 months	37 (45)	7 (32)	
> 18 months	30 (37)	9 (41)	
Patient's Global Assessment (VAS)	36 ± 25†	48 ± 23‡	
Tender joint count	0 (0–3)	1 (1–4)	0.02
HAQ score	0.13 (0.0–0.63)§	0.57 (0.1–0.9)‖	0.07
DAS28	2.5 ± 1.0¶	3.3 ± 0.9‡	0.001
Anti-CarP	80 (0–183)	133 (42–416)	0.04
Anti-CarP positive	10 (12)	7 (32)	0.05
PEth			0.1
None/low consumption	48 (59)*	18 (82)	
Moderate consumption	28 (34)*	3 (14)	
High consumption	5 (6)*	1 (5)	

Data are shown as mean ± sd, n (%), or median (interquartile range).
*n = 81, †n = 79, ‡n = 20, §n = 53, ‖n = 12, ¶n = 78.
RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide antibodies; anti-CarP, anti-carbamylated protein antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; VAS, visual analogue scale; HAQ, Health Assessment Questionnaire; DAS, Disease Activity Score; PEth, phosphatidyl ethanol.
Numerical variables were analysed using the Mann–Whitney U-test and categorical variables by Fisher's exact test or Pearson chi-square.

autoantibody positivity and RF strata were analysed in separate multivariable Cox regression analyses with the adjustments obtained in the univariable analyses. Since seven patients were prescribed disease-modifying anti-arthritic drugs (DMARDs) or oral corticosteroids despite no confirmed arthritis upon clinical examination, we performed a sensitivity analysis excluding these patients. SPSS version 25 (IBM Corp., Armonk, NY, USA) was used for the analyses. Two-sided p-values < 0.05 were considered statistically significant.

Results

PEth

Among patients without baseline arthritis, PEth levels were numerically higher in patients who subsequently progressed compared to those who did not (Figure 2), although this did not reach statistical significance (p = 0.4). Furthermore, PEth levels among those with baseline arthritis were not significantly different compared to those without arthritis at baseline and during follow-up (p = 0.3), but trendwise were lower compared to those who subsequently developed arthritis (p = 0.05) (Figure 2). PEth levels categorized into none/low and moderate/high alcohol consumption did not significantly differ between these three patient categories (p > 0.05 for all comparisons).

Arthritis development

Among the 82 patients without arthritis at inclusion, 39 (48%) developed at least one arthritis during follow-up after a median of 6 months (IQR 3–24 months). Of these 39 patients, 16 (41%) presented with monoarthritis (12 small joints, four large joints), while 23 (59%) had more than one arthritis (all with small joint involvement) at the time of clinical assessment. Baseline ACPA levels, RF status, anti-CarP status, CRP levels, ESR, and DAS28 significantly predicted arthritis development (Table 2), while PEth levels categorized into none/low, moderate, or high alcohol consumption did not (Table 2).

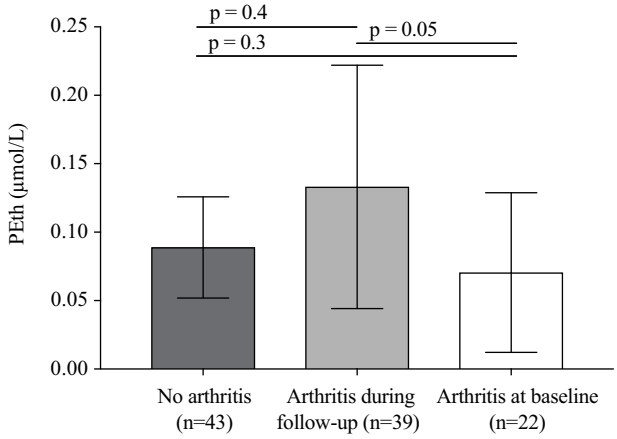

Figure 2. Mean phosphatidyl ethanol (PEth) levels as measured in baseline whole blood samples by liquid chromatography coupled with tandem mass spectrometry in subgroups of TIRx patients. Bars denote mean with 95% confidence interval, analysed using the Mann–Whitney U-test.

ACPAs and RF

Multivariable analysis identified RF status and ACPA levels as independent predictors of arthritis development (Table 2). In addition, we tested ACPA levels categorized into low and high levels according to the 2010 ACR/EULAR criteria, without significant difference regarding arthritis development [high vs low positive; hazard ratio (HR) = 1.5, 95% confidence interval (CI) 0.7–3.3, p = 0.3].

We also categorized patients according to baseline RF levels (negative < 30 U/mL, low positive 30–90 U/mL, and high positive > 90 U/mL). During follow-up, 23 out of 58 RF-negative patients (40%) developed clinical arthritis, compared to seven out of 14 (50%) among low-level positive RF patients, and nine out of 10 (90%) among high-level positive patients (Figure 3). The rate of progression to arthritis in patients with high-level RF was significantly increased compared to both RF-negative patients (HR = 5.4, 95% CI 2.4–12, p < 0.001) (Figure 3) and low-level positive patients (HR = 5.3, 95% CI 1.3–22, p = 0.02). High-level RF remained a significant predictor even after adjusting for ESR, CRP, DAS28, and ACPA levels (Supplementary table S1).

Antibody repertoire

We also investigated the risk of progression in relation to the pattern of autoantibodies present (Figure 4). The presence of ACPAs plus RF was associated with significantly increased risk compared to ACPAs alone (HR = 2.3, 95% CI 1.1–4.6, p = 0.027), whereas ACPA plus anti-CarP-positive patients had no significantly increased HR (2.6, 95% CI 0.8–8.6, p = 0.13). Triple-positive patients had the highest HR compared to ACPA alone (HR = 4.1, 95% CI 1.4–12, p = 0.011), but this did not remain significant after adjusting for ESR, CRP, DAS28, and ACPA levels (Supplementary table S2). RF levels were not significantly higher among anti-CarP-positive compared to anti-CarP-negative patients (p = 0.097).

In a sensitivity analysis excluding patients who started treatment without arthritis having been confirmed, both ACPA levels and RF status remained significant independent predictors, and anti-CarP was also associated with arthritis development in this subset (HR = 3.4, 95% CI 1.0–11, p = 0.046).

Discussion

In this prospective long-term follow up of ACPA-positive patients with musculoskeletal pain but no arthritis at baseline, we found autoantibodies to be major predictors of progression to clinical arthritis. This finding may improve individualization of follow-up strategies and therapy decisions in RA pre-phases. In this study, 48% of the patients progressed to clinical arthritis during a median follow-up of about 6 years. This number is fairly similar to a UK cohort of ACPA-positive patients with musculoskeletal complaints, where 50% developed clinical arthritis (7), and a Dutch cohort of ACPA- or RF-positive arthralgia, where 35% progressed (6). Thus, from this first prospective study on at-risk patients from a Nordic country, we conclude that possible differences in genetic background or lifestyle factors do not translate into significantly altered progression rates.

We found that ACPA levels and RF status are independently associated with progression to clinical arthritis, and high-level positive RF patients face higher risk than those who are low-level RF positive. Further, there was a trend towards higher risk among patients with anti-CarP and triple positivity, i.e. ACPA, RF, and anti-CarP, although it did not remain statistically significant after adjustments. Still, this is in line with a recent meta-analysis reporting high specificity and low sensitivity concerning triple positivity in RA (41). Taken together, the results of the current study suggest a dose–response relationship between autoantibodies, in terms of both levels and types of autoantibodies involved, and the risk of progression to clinical arthritis. Hazard ratios in the current study were in the same range as for pathological ultrasonographic findings in a similar patient population (42), and the magnitude of the autoantibody response may complement imaging techniques when identifying subgroups of arthralgia patients where very early pharmacotherapy should be evaluated in clinical trials.

Routine laboratory markers of inflammation, i.e. ESR and CRP, were associated with arthritis development in univariable analysis, but did not confer independent prognostic value when autoantibodies were included in a multivariable model. This is of interest considering pathogenic mechanisms. In biobank studies on asymptomatic individuals subsequently developing RA, it was shown

Table 2. Cox regression analyses with clinical arthritis development as outcome.

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age	1.0 (0.99–1.1)	0.072		
Female gender	1.1 (0.5–2.5)	0.80		
Smoking				
Non-smoker	Reference			
Former smoker	0.9 (0.5–1.9)	0.87		
Current smoker	1.2 (0.5–2.7)	0.75		
PEth category				
No/low consumption	Reference			
Moderate consumption	1.2 (0.6–2.4)†	0.56		
High consumption	1.7 (0.5–5.7)†	0.40		
Symptom duration				
0–6 months	Reference			
6–18 months	0.6 (0.3–1.4)	0.26		
> 18 months	0.8 (0.3–1.8)	0.58		
Global VAS	1.0 (1.0–1.02)‡	0.13		
Tender joint count	1.1 (1.0–1.1)	0.16		
HAQ score	1.3 (0.6–3.0)§	0.48		
DAS28	1.4 (1.0–1.9)||	0.030*	1.3 (0.9–1.9)¶	0.13
CRP level	1.06 (1.0–1.1)	0.001*	1.0 (0.9–1.0)¶	0.35
ESR	1.04 (1.0–1.1)†	0.019*	1.0 (1.0–1.1)¶	0.37
Shared epitope positive	0.9 (0.5–1.7)†	0.71		
RF positive	2.3 (1.2–4.4)	0.010*	2.3 (1.1–4.8)¶	0.028*
RF levels	1.0 (1.003–1.007)	< 0.001*		
RF				
Negative	Reference			
Low	1.4 (0.6–3.2)	0.48		
High	5.4 (2.4–12)	< 0.001*		
ACPA levels	1.0 (1.000–1.001)	< 0.001*	1.0 (1.000–1.001)¶	0.002*
Anti-CarP positive	2.6 (1.1–5.9)	0.025*	1.6 (0.6–4.6)¶	0.38
Anti-CarP levels	1.0 (1.000–1.003)	0.047*		
Anti-CarP				
Negative	Reference			
Low	2.6 (1.1–5.9)	0.025*		
High	–			
Number of antibodies				
1	Reference			
2	2.3 (1.2–4.5)	0.015*		
3	4.1 (1.4–12)	0.011*		

†n = 81, ‡n = 79, §n = 53, ||n = 78, ¶n = 78.
PEth, phosphatidyl ethanol; VAS, visual analogue scale; HAQ, Health Assessment Questionnaire; DAS, Disease Activity Score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; anti-CarP, anti-carbamylated protein antibodies; HR, hazard ratio; CI, confidence interval.
*Significant association ($p < 0.05$).

that autoantibodies were more important than circulating markers of inflammation in predicting RA development (43, 44). The current study, which involved symptomatic patients closer to disease development, also found that autoantibodies appear more closely associated with progression to arthritis. Furthermore, very limited inflammatory findings were reported in synovial biopsies from autoantibody-positive patients prior to clinical arthritis onset (45). Taken together, it appears that autoantibodies are more decisive in RA pre-phases and that the weighting of autoantibodies versus inflammatory markers in the 2010 classification criteria is well aligned with pathogenesis.

Surprisingly, no clinical variables were associated significantly with arthritis development. It should be noted, however, that some potentially important aspects were not registered in the study; for instance, pain characteristics (e.g. clinically suspect arthralgia), morning stiffness, and body mass index. Alcohol consumption was not obtained from questionnaires, but instead biochemically assessed by analysis of PEth in blood. This approach has the advantage of being free from recall bias, but the disadvantage of reflecting only the month before sampling. We found no support for recent alcohol consumption reducing the risk of progression to clinical arthritis in at-risk patients. This is in line with results from an ACPA-positive UK at-risk cohort (7), but contrasts with an RF- or ACPA-positive cohort from the Netherlands (22). Whether

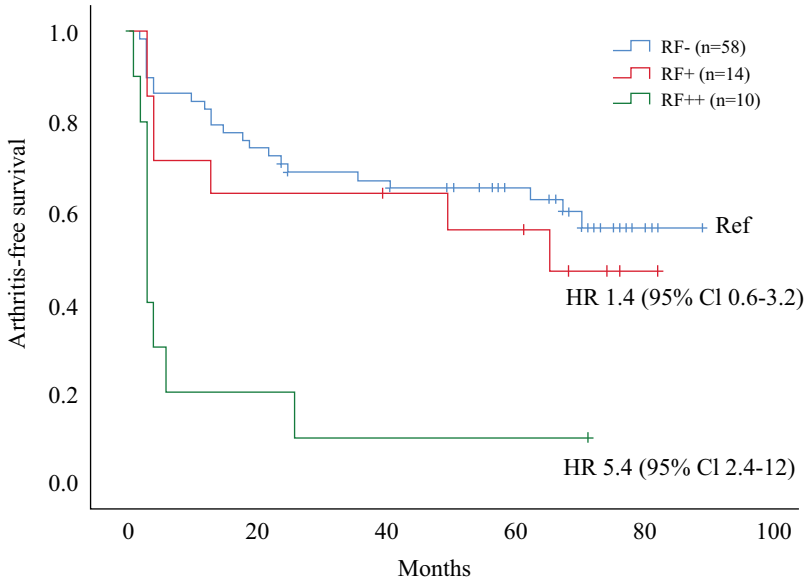

Figure 3. Rheumatoid factor level categories versus progression to clinical arthritis. RF–, rheumatoid arthritis negative; RF+, RF low level; RF++, RF high level. Hazard ratio (HR) with 95% confidence interval (CI) in Cox regression analysis.

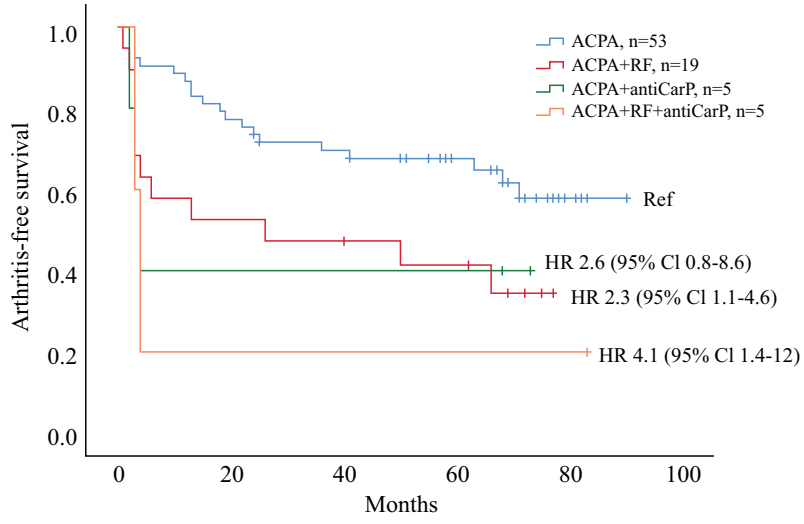

Figure 4. Autoantibody pattern [anti-citrullinated protein antibodies (ACPA), rheumatoid factor (RF), anti-carbamylated protein antibodies (anti-CarP)] at baseline versus progression to clinical arthritis. All patients tested positive for ACPAs. Hazard ratio (HR) with 95% confidence interval (CI) in Cox regression analysis.

these differing results relate to the serological differences of the cohorts is not obvious, but we conclude that alcohol consumption estimation by PEth analysis does not confer valuable information for risk stratification in an ACPA-positive at-risk population.

This study has limitations; for practical reasons, clinical arthritis development was not confirmed by ultrasound or clinically by a second independent investigator. However, all investigators were experienced, and patients were examined by the same rheumatologist at the majority of visits. Another drawback is that, since the study was designed before the launch of the 2010 classification criteria, these were not included as a secondary outcome. Nevertheless, since all patients were ACPA positive and achieved 6 weeks' duration, most patients who progressed to arthritis would fulfil the 2010 criteria. Strengths of this study are the prospective design and the long-term follow-up.

Conclusion

This study confirms that patients with ACPAs and musculoskeletal symptoms are at high risk of developing clinical arthritis, and the magnitude of the autoantibody response appears to be a key determinant of progression.

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Disclosure statement

AK was employed by Sanofi Genzyme in 2018, and has received speaker's fees and honoraria from BMS, Pfizer, Roche, and UCB. LAT is listed as an inventor on a patent describing the methods to detect anti-CarP antibodies. The other authors have no potential conflicts of interest to declare.

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Supporting information

Additional supporting information may be found in the online version of this article.

Supplementary table S1. Multivariable Cox regression analysis of rheumatoid factor strata with clinical arthritis development as outcome (n = 78).
Supplementary table S2. Multivariable Cox regression analysis of different antibody patterns with clinical arthritis development as outcome (n = 78).

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