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Enriching case selection for imminent RA – the use of anti-CCP antibodies in individuals with new nonspecific musculoskeletal symptoms: a cohort study

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Abstract

Objectives

Around 1% of the population test positive for anti-cyclic citrullinated peptide (anti-CCP) antibodies. This biomarker predicts progression to rheumatoid arthritis (RA) but over a variable time-frame. To increase its clinical relevance, this study sought to determine (1) if the proportion of anti-CCP positive individuals could be enriched by case selection of people attending primary care with new nonspecific musculoskeletal (MSK) symptoms but without clinical synovitis (CS) and (2) whether these individuals progress rapidly to inflammatory arthritis (IA), in particular RA.

Methods

In this prospective cohort study, individuals age ≥18 years with new nonspecific MSK symptoms, without CS, were recruited from primary care in the U.K. Anti-CCP positive individuals were invited for follow-up in the rheumatology department, Leeds. Those who tested negative were sent questionnaires 12 months later.

Results

2028 individuals were recruited. Of these 2.8%(57/2028) were anti-CCP positive, of whom 47%(27/57) developed IA ,24 RA (also 1 undifferentiated IA (UIA), and 2 polymyositis); 92.6%(25/27) within 12 months, median 1.8 months(IQR 1.0-4.3, range 0.3 to 16.1). Of the anti-CCP negative individuals, 1.3% (20/1559) developed IA (1 UIA, 13 RA, 6 psoriatic arthritis); 75%(15/20) within 12 months. The RR for developing RA within 12 months in the anti-CCP positive group was 66.8(32.2-138.4, $p<0.001$); for IA it was 45.5(95%CI 25.4-81.6, $p<0.001$).

Conclusion

Selecting individuals with new nonspecific MSK symptoms without CS enriched the prevalence of anti-CCP positivity to 2.8%. Those who tested positive had a high risk of rapidly developing RA. The cost effectiveness of this approach will need to be determined.

From cross sectional studies, anti-cyclic citrullinated peptide antibodies (anti-CCP) are present in approximately one percent of the population.[1 2] Their presence has been associated with a high risk of subsequent development of rheumatoid arthritis (RA). [3 4] Anti-CCP antibodies however can be detected more than 10 years prior to disease onset.[5] The risk of progression to RA in anti-CCP positive individuals from the general population has been estimated at 5% over a 5 year period, [1] meaning that this test is unlikely to be of value as a screening tool. In the years just prior to diagnosis, however, retrospective studies have found the predictive value of CCP testing to be much higher, with a positive predictive value (ppv) of 85% noted within 1.5 years of symptom onset.[5]

It is also recognised that people with RA often have musculoskeletal (MSK) complaints which may not be sufficiently suggestive of an inflammatory arthritis (IA) (from herein referred to as "nonspecific symptoms") in the months or years prior to development of RA. Joint pain, muscle cramps, stiffness, loss of motor control and weakness are described as the first symptoms in people with RA and anti-CCP positive arthralgia.[6] The majority of people present to their general practitioners (GPs) first. It has been estimated that people with RA visited their GPs on average four times before being referred to a specialist for a diagnosis.[7] Identifying individuals with new nonspecific symptoms with the anti-CCP antibody may therefore provide an enriched case selection for imminent RA.

In 2009, the National Audit Office estimated the prevalence of RA in adults in England at 580 000 with an incidence of 26 000 new cases per year.[7] The estimated cost of RA to the UK National Health Service was approximately £560 million a year and the cost of work-related disability and sick leave was estimated at £1.8 billion a year. Delays in treatment have been associated with increased joint damage and poorer function. [8 9]In contrast, early identification has been associated with improved clinical outcomes, health-related quality of life and work ability.[10] Thus very early identification and targeted treatment of individuals at risk of imminent RA[11] has the potential to be cost effective.

In this study we aimed to show that individuals present with new-onset, nonspecific MSK complaints in the pre-clinical phase of RA, and that these individuals can be identified by performing an anti-CCP antibody test. This should identify anti-CCP positive individuals at risk of rapid progression to RA who would otherwise not be referred, allowing assessment of individuals at risk of IA at the earliest opportunity.

The primary hypothesis was that a higher proportion of individuals with new-onset nonspecific MSK symptoms have anti-CCP antibodies compared to the general population. The secondary hypothesis was that the presence of the anti-CCP antibody in individuals with nonspecific MSK symptoms would help to identify those at risk of rapid progression to RA.

Methods

This was a longitudinal prospective cohort study adopted by the National Institute of Health Research Clinical Research Network (NIHR CRN).[12] It was initially conducted in West, North and North East Yorkshire and later opened to recruitment across the U.K. Individuals were recruited between July 2007 and March 2015. GPs, MSK physicians, physiotherapists, nurse practitioners and other health professionals were asked to refer individuals aged ≥18 years with any new MSK complaint, whom they were not already planning to refer to a rheumatology unit with an IA, for an anti-CCP test. For purpose of this study, a new MSK complaint was defined as any joint/ MSK symptom, including (but not limited to) rotator cuff tendonitis, subacromial bursitis, carpal tunnel syndrome, tendonitis e.g. epicondylitis, which the patient had not previously reported to their GP. Individuals with documented IA were excluded.

Individuals consenting to study participation were instructed to go to their GPs/ local phlebotomy centres to give a blood sample. The serum was sent to Chapel Allerton Hospital, Leeds for the anti-CCP antibody tests to be performed. This was done using second generation CCP assays. Anti-CCP positivity was determined using machine-specific cut-offs - initially using an Immunocap 250 (Phadia) (reference range <7U/mL) and later a Bioplex 2200 (Bio-rad) machine (reference range <2.99 U/mL). They were also asked to complete a questionnaire and provide information on previous or current MSK diagnoses and mark their symptoms on a diagram. The questionnaire was updated during the course of the study to request details for information on family history of RA and smoking.

Individuals with positive anti-CCP antibody test results were contacted by the Rheumatology Department and offered an outpatient appointment at the CCP Clinic at Chapel Allerton Hospital for clinical assessments, blood tests and imaging with X-rays and other modalities. Individuals with negative anti-CCP tests continued to be followed up with their GPs. They were also contacted via telephone/post 12 months after consenting to the study and sent a questionnaire. Follow up was therefore either after a period of 12 months or until the development of clinical synovitis. If necessary, GPs and rheumatology departments were also contacted for relevant diagnoses.

Outcomes

The primary outcome was the proportion of individuals with new-onset nonspecific MSK symptoms who were anti-CCP positive. Secondary outcomes included the number of anti-CCP positive individuals who progressed to IA, in particular RA (according to the 2010 ACR/EULAR RA classification criteria[13]), and the time to IA diagnosis. Other outcomes of interest included the initial presenting complaint of all individuals (anti-CCP positive and negative), as this may help to determine whether there is a symptom complex that would prompt autoantibody testing.

Statistical analysis

Statistical analyses were performed using SPSS 21 and StataIC 13. For the analyses, the date of the anti-CCP test was used as the baseline date. Demographic characteristics, prevalence of anti- CCP positivity, progression to IA and the associations with joint involvement were calculated using Pearson's chi square tests. A one-sample binomial test was used to assess whether the proportion of individuals with anti-CCP antibodies was higher amongst those presenting with new MSK pain compared to the estimated proportion in the general population (1%). Median time to IA development was compared using a log rank test. Sensitivity and specificity for the anti-CCP antibody test were calculated together the 95% confidence intervals (Wilson method). Binary logistic regression was used to assess the association between the involvement of specific joint types and the risk of being anti-CCP positive.

Results

In total 2195 individuals were referred of whom 2028 individuals with new nonspecific MSK symptoms were enrolled (figure 1). The mean age was 49.2 (13.6) years and the majority were female (75.9%). Of these, 2.8% (57/2028) were anti-CCP positive, a significantly higher proportion that the estimated 1% for the general population (95% CI 2.1% to 3.6%, $p<0.001$). There were no differences in demographic features between anti-CCP positive and anti-CCP negative individuals. Individuals had a range of MSK and associated conditions with no significant differences between those who were anti-CCP positive or negative (table 1).

Of those who were antibody positive, 47.4% (27/57) were subsequently diagnosed with an IA – 1 with undifferentiated IA (UA), 24 with RA and 2 with polymyositis. Of those who were tested anti-CCP negative and completed at least 1 year of follow up, 1.3% (20/1559) were diagnosed with an IA – 1 with undifferentiated IA, 13 with RA and 6 with psoriatic arthritis (PsA). The relative risk (RR) for ever developing IA in the anti-CCP positive group was 36.8 (95% CI 22.0 to 61.7, p <0.001 and the RR for developing RA was 50.4 (27.1 to 93.8), p<0.001).(table 2) The sensitivity and specificity for the development of any IA in the anti-CCP positive individuals were 57.4 % (43.3% to 70.5%), and 98.1% (97.3% to 98.7%) respectively, and the ppv and negative predictive value (npv) were 47.4% (35.0% to 60.1%) and 98.7% (98.0% to 99.2%). The sensitivity, specificity, ppv and npv for progression to RA were 64.9% (48.8% to 78.2%), 97.9% (97.1% to 98.5%), 42.1% (30.2% to 55.0%) and 99.2% (98.6% to 99.5%) respectively.

Median duration of follow up of anti-CCP positive individuals with MSK symptoms (to IA diagnosis or last assessment) was 11.5 months (IQR 1.5 to 28.2; range: 0.3 to 79.1 months). The median time for progression to IA in the 25 anti-CCP positive individuals was 1.8 months (95% CI: 1.2 to 2.3, IQR 1.0-4.3, range 0.3 to 16.1). The majority (25/27 (92.6%)) were diagnosed within 12 months of the anti-CCP test. In the anti-CCP negative individuals, median time to IA diagnosis or last follow up was 13.8 months (IQR: 12.5; 21.5, range 1.2 to 84.4 months) and median time to IA diagnosis was 5.1 months (95% CI: 4.2 to 5.8; IQR 2.9; 13.5, range 1.2 to 27.2, p=0.002 for anti-CCP positive vs. anti-CCP negative); 75% (15/20) were diagnosed within 1 year of having the test. The RR for developing IA within 12 months in the anti-CCP positive group was 45.5 (25.4 to 81.6), p<0.001 and RR for developing RA within 12 months: 66.8 (32.2 to 138.4), p<0.001). (figure 2)

Analyses of location of symptoms, showed that individuals with pain affecting the regions of the wrists and/or hands or the feet were more likely to be anti-CCP positive (RR 2.9 (1.2 to 7.3, p=0.024) for wrists and/or hands and RR 2.1 (1.2 to 3.6, p=0.008) for feet). Those with shoulder symptoms were also more likely to have a positive anti-CCP result (RR 2.1 (1.2 to 3.7, p=0.010)). (table 3) The association between the location of symptoms and progression to RA was not analysed as the number of patients per variable would be too small.[14 15]

Discussion

To our knowledge this is the first prospective cohort study addressing the prevalence of anti-CCP in individuals with new nonspecific MSK symptoms without clinical synovitis and the progression to IA.

In this cohort of individuals referred from primary care, 2.8% were anti-CCP antibody-positive with 45% progressing to IA mainly RA, the majority within one year or antibody testing.

Several retrospective studies have identified the presence of RA associated autoantibodies in individuals with RA prior to disease onset with a rise in prevalence in the years just prior to diagnosis. [1 5] In a large population study, the prevalence of RA was found to be 19% in rheumatoid factor (RF) positive individuals.[16] Finding from the Nurses' Health Study showed a sensitivity and specificity of 28% and 100% respectively in a single pre-RA diagnosis serum sample tested for anti-CCP antibodies. Higher antibody levels were associated with a shorter time to diagnosis. [17] In another cohort of 147 individuals with arthralgia without IA, of whom 50 were CCP positive, 52 RF positive and 45 positive for both antibodies, 45% developed RA after a median 28 months. The presence of anti-citrullinated protein antibodies (ACPA), but not RF or shared epitope, was associated with disease progression. [18]

In recent years, there has been increasing focus on work addressing individuals at risk of developing RA.[19] Other methods have also been evaluated for identifying these individuals early. Liang et al. have explored the possibility of an internet-based method for identifying people with symptoms of an inflammatory polyarthritis of less than 12 weeks. In this study, 43 244 people took the online questionnaire.[20] Of these 60 took a self-scoring algorithm for IA, 48 screened positive, 24 were evaluated and 3 diagnosed with IA. Of the 24 people, 17 completed a follow up questionnaire at 1 year – 3 were diagnosed with RA and were on methotrexate.

An important question that would need careful consideration prior to implementing any case finding strategy is that of cost –effectiveness. On the one hand, there is the cost of the disease, which is associated with irreversible joint damage and increased morbidity, the cost of treatment and societal costs including potential job loss.[7] This needs to be balance against the cost of performing investigations in order to finding early treatable RA and preventing disease progression.

Testing of individuals with nonspecific symptoms for anti-CCP provides a relatively easy and simple method for identifying individuals at risk at an early stage. Another possibility would be to refine the group to be tested and referred. Hand involvement has been reported to be more common in individuals who progress to RA. [6] In our cohort, symptoms involving the wrists and/or hands, feet and the shoulders were associated with anti-CCP positivity. A history of early morning stiffness (EMS), the presence of polyarticular pain, RF or inflammatory markers has been reported to increase

the positive predictive value of anti-CCP in individuals with early RA.[21] In another cohort, ACPA positive individuals with symmetric arthralgia of small joints and EMS, 60% progress to RA.[18] The presence of anti- CCP together with inflammatory symptoms, the presence of shared epitope and imaging with ultrasound have been shown enable identification of individuals with RA at an early stage.[11]

Whilst the majority of anti-CCP positive individuals who progressed to IA in this cohort were classified as RA, two individuals were later diagnosed with Jo-1 polymyositis, one with high level anti-CCP antibodies and one with a borderline result. Studies suggest that the autoimmune process in ACPA-associated diseases may begin at mucosal sites e.g. the lung.[22] These two individuals may have an overlap of RA and polymyositis. The possibility of a pathogenic link between polymyositis and ACPA with lung involvement in both, however, is an interesting one.

The study has its limitations. These findings have been compared to an estimated 1% based on blood donor cohorts.[1 2] Whilst this may be a reasonable approximation of anti-CCP positivity in the general population, it is known that screening of donors exclude individuals with medical conditions and may therefore underestimate the population prevalence of the antibody. Despite this, findings from this study suggest that individuals with rapid progression to RA may be identified. Another limitation is that participants in this study have mainly been recruited from Yorkshire, U.K. The antibody prevalence may differ in other populations and ethnic groups. Of the individuals who progressed to RA, approximately one third were anti-CCP negative. Whilst anti-CCP positivity has been associated with more severe destructive disease, the study confirms the need for additional biomarkers for the diagnosis of seronegative RA and other inflammatory arthritides e.g. PsA. The joint symptoms and associated conditions were all self-reported from patient questionnaires. It is possible that there may be a bias towards under-reporting as patients may have only reported what they may have perceived as relevant to this study.

In conclusion, in our study selecting individuals with new nonspecific MSK symptoms without clinical synovitis enriched the prevalence of anti-CCP positivity to 2.8%, with anti-CCP positive individuals being found to be at high risk of rapidly developing an inflammatory arthritis, in particular RA. The cost-effectiveness of this approach will need to be determined.

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Figure 1. Study recruitment

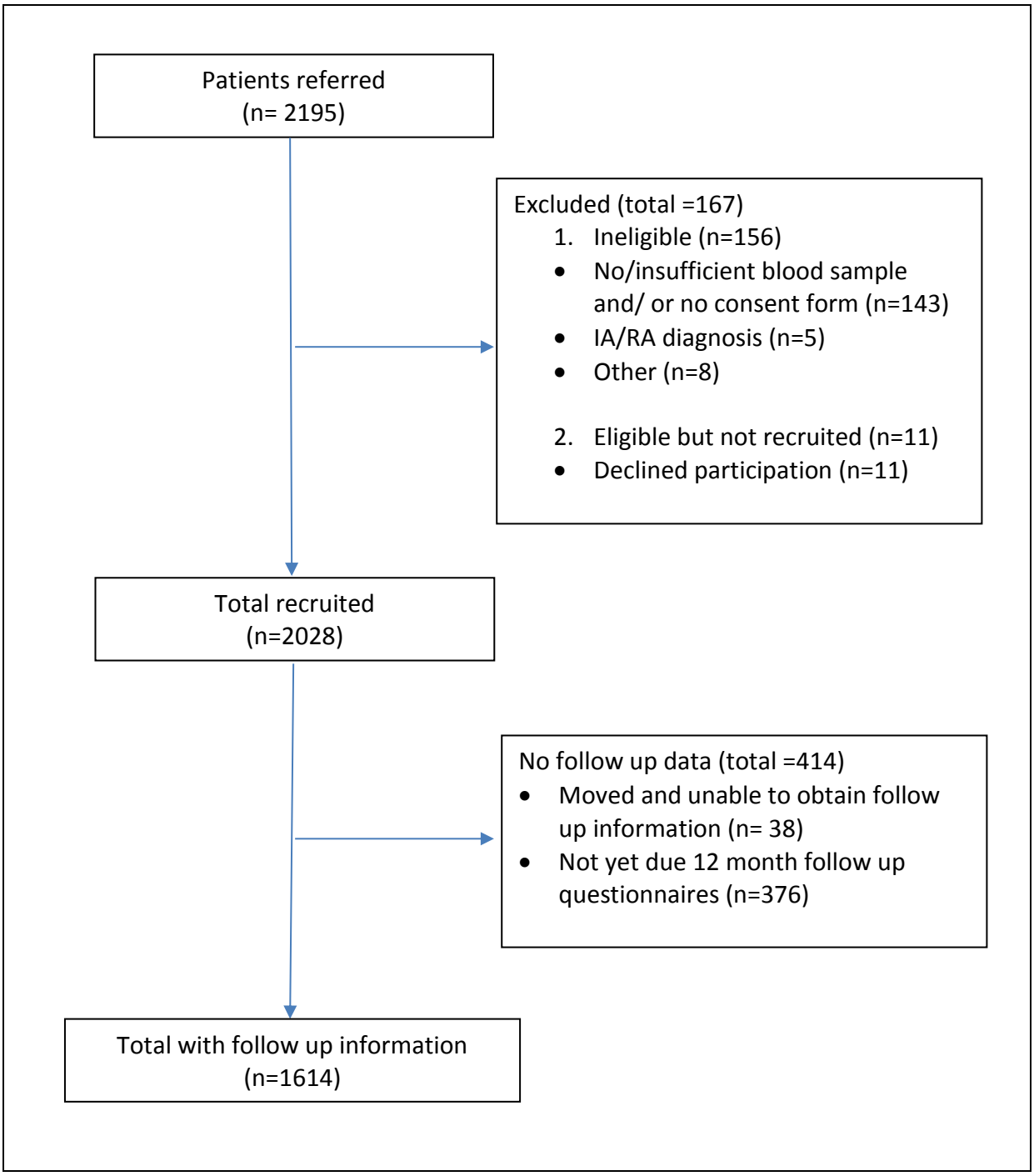


Table 1. Baseline characteristics of individuals with new non-specific MSK symptoms

Characteristic	**Anti-CCP negative (n=1971)**	**Anti-CCP positive (n=57)**	**p**
Female (n)	76.2% (1502)	66.7% (38)	0.097
Age (years) mean (SD; range)	49.2 (13.6; 18-90)	49.2 (13.3; 24-80)	0.986
RA FDR (n (%))	32.0% (369/1153)	28.0% (14/50)	0.552
Smoker - Never smoked - Ex-smoker - Current smoker	 50.6% (171/338) 33.1% (112/338) 16.3% (55/338)	 34.6 % (18/52) 48.1% (25/52) 17.3% (9/52)	0.072
Current or previous diagnoses			
Osteoarthritis/ multiple mechanical joint pain	17.6% (337/1917)	9.1% (5/55)	0.101
Gout	1.0% (20/1917)	1.8% (1/55)	0.581
Hypermobility	0.7% (14/1917)	0% (0/55)	0.525
Arthralgia/ Arthritis NOS/ other joint problems	5.4% (103/1917)	1.8% (1/55)	0.245
Tendinopathies including rotator cuff tendonitis, tennis elbow/golfer's elbow and trigger finger	24.4 % (468/1917)	21.8% (12/55)	0.658
Nerve entrapment e.g. CTS	13.1% (252/1917)	7.3% (4/55)	0.201
Bone conditions e.g. osteoporosis	0.7% (14/1917)	0% (0/55)	0.525
Polymyalgia rheumatica	0.3% (5/1917)	0% (0/55)	0.705
Fibromyalgia	1.3% (25/1917)	0% (0/55)	0.394
Muscular pain	0.6% (11/1917)	0% (0/55)	0.573
*Other conditions e.g. Crohn's disease	2.1% (40/1917)	5.5% (3/55)	0.092

Values presented are % (n/N) unless indicated otherwise.

Anti-CCP, anti-cyclic citrullinated peptide; CTS, carpal tunnel syndrome; FDR, first degree relative; MSK, musculoskeletal; NOS, not otherwise specified; RA, rheumatoid arthritis; * other self-reported diseases from patient questionnaires which included diagnoses of hypothyroidism, chronic fatigue syndrome, Raynaud's phenomenon, Crohn's disease and vitamin B12 deficiency.

Table 2. Outcomes of anti-CCP positive and negative individuals with new nonspecific MSK symptoms

	Anti-CCP negative (n=1557)*	Anti-CCP positive (n=57)
No IA % (n)	98.7% (1537)	52.6% (30)
UIA % (n)	0.1% (1)	1.8% (1)
RA % (n)	0.8% (13)	42.1% (24)
PsA or IA with Psoriasis % (n)	0.4% (6)	0% (0)
CTD % (n)	0% (0)	3.5% (2)

IA, inflammatory arthritis; RA, rheumatoid arthritis; PsA, psoriatic arthritis; UIA, undifferentiated inflammatory arthritis; *patients who have reached their 12 month follow-up time point (1557/1971)

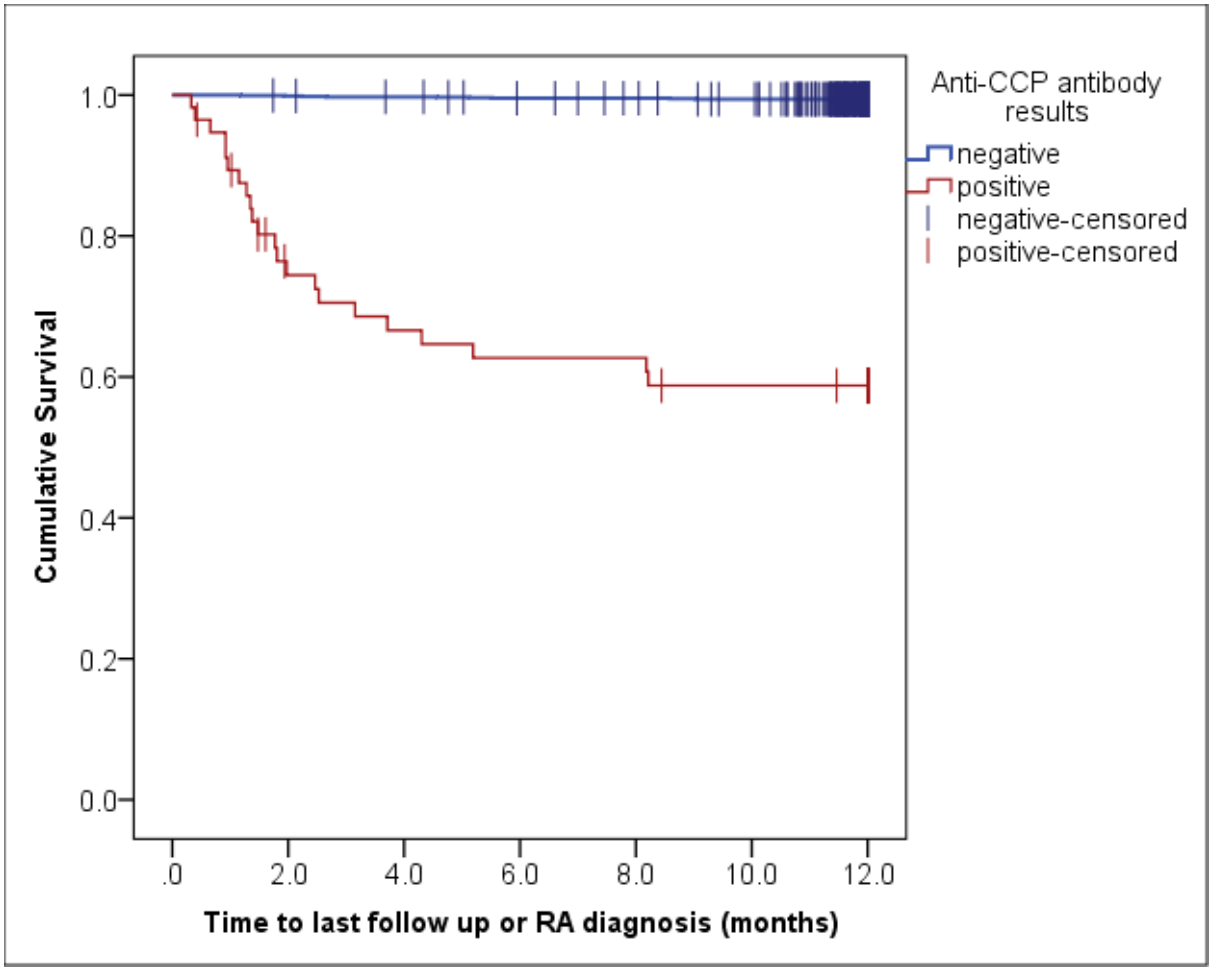
Table 3. Associations between joint symptoms and anti-CCP positivity in individuals with new nonspecific MSK symptoms

Joint involved		**% (n/N) who are anti-CCP positive**	**Model RR (95% CI), p**
Neck	Absent	2.9% (40/1364)	reference
	Present	2.5% (15/608)	0.9 (0.5, 1.6); p=0.627
Back	Absent	3.6% (48/1352)	reference
	Present	1.1% (7/620)	0.3 (0.1, 0.7);p=0.008
R or L shoulder	Absent	2.2% (25/1116)	reference
	Present	3.5% (30/856)	2.1 (1.2, 3.8);p=0.010
R or L elbow	Absent	3.1% (40/1297)	reference
	Present	2.2% (15/675)	0.7 (0.4, 1.2);p=0.184
R or L wrist and/or hand	Absent	1.0% (5/483)	reference
	Present	3.4% (50/1489)	2.9 (1.2, 7.3);p=0.024
R or L hip	Absent	3.4% (41/1208)	reference
	Present	1.8% (14/764)	0.6 (0.3, 1.1); p=0.075
R or L knee	Absent	3.3% (28/836)	reference
	Present	2.4% (27/1136)	0.8 (0.5, 1.4);p=0.442
R or L ankle	Absent	3.1% (41/1333)	reference
	Present	2.2% (14/639)	0.8 (0.4, 1.4);p=0.377

R or L foot	Absent	2.2% (27/1224)	reference
	Present	3.7% (28/748)	2.1 (1.2, 3.6); p=0.008

L, left; MSK, musculoskeletal symptoms, R, right

Figure2. Kaplan-Meier graph: Time to RA progression in anti-CCP positive and anti-CCP negative individuals with MSK symptoms



anti-CCP, anti-cyclic citrullinated peptide antibody; RA, rheumatoid arthritis; MSK, musculoskeletal symptoms

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