**Table S1: Important variables contributing to the two latent factors identified in PLS analysis**

|  |  |  |
| --- | --- | --- |
|  | **Latent factor 1** | **Latent factor 2** |
| ***Time of initial symptoms***Symmetric onset of symptomsInitial symptoms in large jointsInitial symptoms both in small and large jointsInitial symptoms in upper extremitiesInitial symptoms both in upper and lower extremities | 1.1521.1631.563 | +-+ | 1.2121.1421.0611.0811.435 | ---+- |
| ***Presentation with arthralgia***Inflammatory type of symptomsMorning stiffness≥60 minutesSymptom durationDifficulties making a fistPositive squeeze test MTP-jointsTender joint count | 1.3161.7971.4132.0831.0911.609 | +-+--- | 1.2571.7341.3652.0671.0161.479 | --+--+ |
| **Variance explained** | 43.0% | 8.3% |

The variable importance in the projection (VIP) is depicted here. Generally VIP-values >1.0 are considered relevant (only these are shown here). Together these two factors explain 51.3% of the observed variance between ACPA-positive and ACPA-negative patients. The +/- sign shows whether this variable led to a higher score (+) on this factor, or to a lower score (-).

**Table S2: Clinical characteristics of ACPA-negative and ACPA-positive patients in the symptomatic phase preceding clinical arthritis; sub-analysis in patients who fulfilled the 2010-criteria for RA and/or were started on DMARD-therapy at the time of arthritis development.**

|  |  |  |
| --- | --- | --- |
|  | **All patients** |  |
|  | **ACPA-negative (n=30)** | **ACPA-positive (n=29)** | **p-value** |
| **Symptoms at symptom onset***Symptom onset* -Acute (<1 week) -Gradual -Intermittent*Symptoms started with\** Pain Stiffness Loss of function*Localization affected joints* -Small joints hand/feet -Large joints -Both*Localization affected joints* -Upper extremities -Lower extremities -Both*Localization affected joints* -Symmetric  | 6 (20)22 (73)2 (7)27 (90)22 (73)13 (43)22 (73)4 (13)4 (13)24 (80)5 (17)1 (3)19 (63) | 7 (24) 16 (57)5 (18)29 (100)16 (55)10 (35)21 (72)1 (3)7 (24)14 (48)4 (14)11 (38)21 (72) | 0.520.820.150.490.27**0.004**0.46 |
| **Presentation with arthralgia***Family history of RA**Symptoms determining inclusion in the cohort* -Inflammatory type of symptoms -Morning stiffness ≥60 minutes -Both*Physical examination* 68-TJC, mean±SD Difficulty making a fistSqueeze test -Positive for both MTP- and MCP-joints -Positive for MCP-joints only -Positive for MTP-joints only -Negative for both*Additional investigations**HAQ-score, mean±SD* | 12 (40)11 (38)8 (28)10 (35)9±813 (43)7 (24)9 (31)4 (14)9 (31)0.8±0.6 | 11 (38)17 (59)2 (7)10 (25)4±33 (11)4 (14)7 (25)2 (7)15 (54)0.7±0.5 | 0.870.087**0.012****0.007**¥0.360.61 |

All values are indicated as n(%), unless indicated otherwise.

\*Multiple answers could be given, so the percentages can add up to >100%

¥Significant after correction for multiple testing.

ACPA; anticitrullinated protein antibodies, SD; standard deviation, RA; rheumatoid arthritis, DMARD; disease modifying antirheumatic drug, TJC; tender joint count, MCP; metacarpophalangeal, MTP; metatarsophalangeal, HAQ; health assessment questionnaire

Missings were as follows: symptom onset (1), symptoms determining inclusion in the cohort (1), difficulties making a fist (2), squeeze test (2), HAQ-score (2)

**Table S3: Clinical characteristics of patients in the symptomatic phase preceding clinical arthritis, stratified for ACPA and RF**

|  |  |  |
| --- | --- | --- |
|  | **All patients** |  |
|  | **ACPA-/RF- (n=30)** | **ACPA-/RF+ (n=7)** | **ACPA+/RF- (n=3)** | **ACPA+/RF+ (n=27)** | **p-value** |
| **Symptoms at symptom onset***Symptom onset* -Acute (<1 week) -Gradual -Intermittent*Symptoms started with\** Pain Stiffness Loss of function*Localization affected joints* -Small joints hand/feet -Large joints -Both*Localization affected joints* -Upper extremities -Lower extremities -Both*Localization affected joints* -Symmetric  | 7 (23)20 (67)3 (10)28 (93)21 (70)13 (43)23 (77)3 (10)4 (13)22 (73)5 (17)3 (10)19 (63) | 1 (14)6 (86)0 (0)6 (86)5 (71)3 (43)4 (57)2 (29)1 (14)7 (100)0 (0)0 (0)3 (43) | 2 (67)1 (33)0 (0)3 (100)0 (0)0 (0)1 (33)0 (0)2 (67)1 (33)0 (0)2 (67)2 (67) | 6 (23)15 (58)5 (19)26 (96)17 (63)10 (37)20 (74)1 (4)6 (22)14 (52)4 (15)9 (33)7 (26) | 0.510.72 0.110.520.16**0.050**0.47 |
| **Presentation with arthralgia***Family history of RA**Symptoms determining inclusion in the cohort* -Inflammatory type of symptoms -Morning stiffness ≥60 minutes -Both*Physical examination* 68-TJC, mean±SD Difficulties making a fist Squeeze test -Positive for both MTP- and MCP-joints -Positive for MCP-joints only -Positive for MTP-joints only -Negative for both*HAQ-score, mean±SD* | 9 (30)10 (33)8 (27)12 (40)10±815 (50)7 (24)9 (31)3 (10)10 (35)0.9±0.6 | 4 (57)4 (67)1 (17)1 (17)5±21 (14)1 (14)2 (29)1 (14)3 (43)0.6±0.5 | 1 (33)2 (67)0 (0)1 (33)6±50 (0)0 (0)0 (0)1 (33)2 (67)0.1±0.8 | 10 (37)16 (59)2 (7)9 (33)4±33 (12)4 (15)7 (27)1 (4)14 (54)0.7±0.6 | 0.600.30**0.019****0.008**0.420.67 |

All values are indicated as n(%), unless indicated otherwise.

\*Multiple answers could be given, so the percentages can add up to >100%

ACPA; anticitrullinated protein antibodies, RF; rheumatoid factor SD; standard deviation, RA; rheumatoid arthritis, TJC; tender joint count, MCP; metacarpophalangeal, MTP; metatarsophalangeal, HAQ; health assessment questionnaire

Missings were as follows: symptom onset (1), symptoms determining inclusion in the cohort (1), difficulties making a fist (1), squeeze test (2), HAQ-score (2)

**Figure S1: Time from symptom onset to presentation with arthralgia (left part) and from presentation with arthralgia to arthritis development (right part) in patients who fulfilled the 2010-criteria for RA and/or were started on DMARD-therapy at the time of arthritis development**

This graph shows that ACPA-negative patients have a shorter symptom duration at the time of first presentation, but that ACPA-positive patients progress to arthritis more quickly thereafter.
There are three data points that are not shown (but were included in the analysis): two ACPA-positive patients had a symptom duration ≥120 weeks\* and one ACPA-negative patient developed arthritis ≥120 weeks after inclusion in the cohort. Symptom duration was unknown in 1 patient.
\* Symptom duration was based on a self-reported date of onset. If the character of the symptoms changed over time this self-reported date can be different from the date of onset that rheumatologists considered relevant and used for inclusion in the cohort.
RA; rheumatoid arthritis, DMARD; disease modifying antirheumatic drug, ACPA; anticitrullinated protein antibodies.