**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 symptoms  Initial symptoms in large joints  Initial symptoms both in small and large joints  Initial symptoms in upper extremities  Initial symptoms both in upper and lower extremities | 1.152  1.163  1.563 | +  -  + | 1.212  1.142  1.061  1.081  1.435 | -  -  -  +  - |
| ***Presentation with arthralgia***  Inflammatory type of symptoms  Morning stiffness≥60 minutes  Symptom duration  Difficulties making a fist  Positive squeeze test MTP-joints  Tender joint count | 1.316  1.797  1.413  2.083  1.091  1.609 | +  -  +  -  -  - | 1.257  1.734  1.365  2.067  1.016  1.479 | -  -  +  -  -  + |
| **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) | 0.52  0.82  0.15  0.49  0.27  **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 fist  Squeeze 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±8  13 (43)  7 (24)  9 (31)  4 (14)  9 (31)  0.8±0.6 | 11 (38)  17 (59)  2 (7)  10 (25)  4±3  3 (11)  4 (14)  7 (25)  2 (7)  15 (54)  0.7±0.5 | 0.87  0.087  **0.012**  **0.007**¥  0.36  0.61 |

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) | 0.51  0.72  0.11  0.52  0.16  **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±8  15 (50)  7 (24)  9 (31)  3 (10)  10 (35)  0.9±0.6 | 4 (57)  4 (67)  1 (17)  1 (17)  5±2  1 (14)  1 (14)  2 (29)  1 (14)  3 (43)  0.6±0.5 | 1 (33)  2 (67)  0 (0)  1 (33)  6±5  0 (0)  0 (0)  0 (0)  1 (33)  2 (67)  0.1±0.8 | 10 (37)  16 (59)  2 (7)  9 (33)  4±3  3 (12)  4 (15)  7 (27)  1 (4)  14 (54)  0.7±0.6 | 0.60  0.30  **0.019**  **0.008**  0.42  0.67 |

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.