Patients were evaluated at baseline and every 3 months according to prediction rule derived from Leiden Early Arthritis Clinic that includes - TJC and SJC, laboratory indices and disability measured by the Health Assessment Questionnaire and assessment of disease activity by the Disease Activity Score 28 (DAS28) and baseline photographs of small joints of both hands. Fifty-eight patients were enrolled. Eight patients were lost to follow-up and were excluded from final analysis.

The prediction rule consists of clinical variables, which are scored (range: 0–13) and corresponds to the percent chance of developing RA. The rule was applied to baseline characteristics of all patients with UA, who had completed 1-year follow-up to allow sufficient time for diagnosis. After 1 year, all patients were examined to determine if RA or another ACR-defined rheumatological condition had developed or the disease course persisted as UA or had a complete remission (defined as DAS28 ≤2.6).

A small sample size (15 numbers) pilot study was conducted to check the content and appropriateness of the questionnaire. Large sample internal and external validity test were not performed.

Statistical analysis

Collections of data are analyzed, and statistical tests are done with the help of Microsoft Excel, Statistical Package for the Social Sciences (SPSS) /Version 14, Developer: IBM (Chicago, IL, USA).

Patients were divided into two groups: Those who developed RA after 1 year of follow-up and those who did not. Mann–Whitney U-test was performed for ordinal variables (e.g., SJC) and *t*-test was performed for continuous variables (e.g., CRP). Among the variables that showed significant change, TJC, duration of morning stiffness, and duration of arthritis were selected as clinical variables for linear discriminant analysis with disease outcome being the dependent variable. These variables satisfied prerequisites for the analysis. Discriminant scores (D) for each patient was calculated. A receiver operating characteristic (ROC) curve was constructed with the discriminant score and compared with Leiden prediction score.

Results

Table 1 describes the characteristics of fifty UA patients satisfying inclusion criteria. The mean age was 40.3 years and most was female 82% (41/50). All patients had been followed up for 1 year. At follow–up, 54% (27/50) patients were diagnosed with RA, whereas the remainder 46% (23/50) developed other rheumatologic condition or inflammatory arthritis due to viral infection, remained undifferentiated or attained complete remission. Of the patients who did not progress to develop RA (nonprogressors), 2% (1/50) patient was diagnosed with diffuse scleroderma due to subsequent development of skin and other characteristics of the disease as well as Scl-70 positivity. About Eight percent (4/50) patients developed symptoms consistent with postviral arthritis and 4% (2/50) patients with systemic lupus erythematosus (SLE). The largest group (n = 13, 26%) of nonprogressors remained undifferentiated at follow-up.

Patients progressing to RA were more likely to have a positive family history of RA and present with symmetric joint involvement initially. Patients who developed RA also had longer duration of morning stiffness and high inflammatory markers although it was not statistically significant. Factors significantly associated with progression to RA were the TJC and SJC, RF positivity, anti-CCP positivity, high DAS28, longer symptom duration at first presentation as well as longer duration of morning stiffness.

Table 2 shows the number of patients who developed RA in relation to the calculated prediction score, the regression

Table 1: Baseline characteristics of patients with undifferentiated arthritis

	No Progression to RA (*n*=23)	Progression to RA (*n*=27)	*P*
Age, mean (SD) years	40.3 (10.4)	36.7 (10.4)	0.22
Sex, F: M	16:7	25: 2	
Swollen joint count, median	6 (0-14)	8 (0-16)	*P*<0.001
Tender joint count, median	17 (6-28)	18 (8-38)	0.005
RF+ve (percent)	2 (8.7)	14 (51.9)	0.001
Anti CCP titre, mean (SD)	0.65 (0.2)	4.6 (7.9)	<0.02
ESR, mean(SD) mm 1st hour	54.7 (19.6)	58.3 (22.6)	0.55
CRP, mean (SD) mg/L	21.9 (8.3)	19.5 (13.9)	0.47
Morning Stiffness, mean (SD) minutes	33 (29.9)	87.8 (49.9)	*P*<0.001
Symptom duration			
< 1 month (percent)	10 (43.5)	1 (3.7)	P<0.01
1-3 month (percent)	6 (26.0)	13 (48.2)	
> 3 month (percent)	7 (30.5)	13 (48.1)	
DAS 28 mean (SD)	5.66 (1.01)	6.86 (82)	*P*<0.001

Values are shown as number (%) unless stated otherwise. Anti-CCP: Anti-cyclic Citrullinated peptide, DAS28: Disease Activity Score 28, ESR: Erythrocyte sedimentation rate, IQR: Interquartile range, RA: Rheumatoid arthritis, RF: Rheumatoid factor, SD: Standard deviation

coefficients of the predictive variables were rounded to the nearest number ending in 5 or 0. No patients with UA, who scored 4 or less progressed to RA, whereas all who scored 7 or more, did progress]. For those who scored between 4 and 7, higher scores frequently predicted progression [Table 3]. Among progressors, the median prediction score was 9.20 (interquartile range [IQR] 5.52–10.70) while nonprogressor's median score was 5.70 (IQR 2.36–7.2). Thirty-three (66%) patients with UA scored between 5 and 8, and they had confirmed RA by 1-year follow-up.

Mann–Whitney U-test was performed to calculate significance level of SJC and TJC. Significance levels were $P < 0.001$) and $P < 0.01$, respectively.

Unstandardized canonical discriminant coefficients for TJC (T), duration of morning stiffness (M), and duration of arthritis (A) were 0.164, 0.066, and 0.012, respectively. The constant was calculated as −2.838. ROC curve was plotted with the formula:

$$D = 0.164 \times T + 0.066 \times M + 0.012 \times A - 2.838.$$

Area under curve (AUC) at 95% confidence interval for our discriminant function was 0.845 (standard error [SE] 0.054). In comparison, AUC of Leiden prediction score was 0.897 (SE 0.043) [Figure 1].

Table 2: A. Prediction score distribution according to disease outcome (First Visit)

Prediction score	No progression to RA (*n*=23)	Progression to RA (*n*=27)
0	0 (0)	0 (0)
1	0 (0)	0 (0)
2	2 (100)	0 (0)
3	0 (0)	0 (0)
4	3 (100)	0 (100)
5	3 (75)	1 (25)
6	12 (70.6)	5 (29.4)
7	3 (37.5)	5 (62.5)
8	0 (0)	4 (100)
9	0 (0)	3 (100)
10	0 (0)	6 (100)
11	0 (0)	3 (100)
12	0 (0)	0 (0)
13	0 (0)	0 (0)
Median score (IQR)	5.70 (2.36-7.2)	9.20 (5.52-10.70)

Values are the number (%) of patients with a given score. IQR: Interquartile range, RA: Rheumatoid arthritis

Table 3: Cut-off values for prediction scores and risk of development of RA on first visit

Cut-off value	No progression to RA	Progression to RA
<4.0	2 (100)	0 (0)
4.0-7.0	21 (65.6)	11 (34.3)
>7.0	0 (0)	16 (100)

Discussion

RA is the most common inflammatory arthritis, affecting 0.5–1% of the general population.[9] Prevalence of RA is about 0.075% in India.[10] Over the past decade, treatment of RA has been characterized by early, aggressive treatment with DMARDs, because this treatment strategy prevents joint damage and functional disability.[11] In rheumatology clinics, the majority of patients who present with recent onset arthritis have UA, which is a form of arthritis that does not fulfill the classification criteria for a more definitive diagnosis.

With regard to early UA, it was observed that predictive factors for the fulfillment of the 2000 EULAR criteria for RA and for having persistent arthritis were largely similar. Perhaps, of greater clinical utility is the DAS, which provides a composite measure of disease activity based on joint counts ESR and patient global assessment of general health and is also easier to use in the clinics.[12] However, this composite score (DAS) is just a measure of disease activity and cannot predict the development of RA among UA patients. A group of patients from the Amsterdam early arthritis clinic with peripheral arthritis and disease duration of <3 years were followed in order to identify independent predictors of outcome.[13] In this study, 27% of the patients were clinically diagnosed as having UA at inclusion and 72% as RA. After 1-year follow-up, 42% of the patients were diagnosed as RA, but no individual predictor was found. Leiden Early Arthritis Clinic included patients with any form of arthritis <2 years duration confirmed by a rheumatologist. Out of 936 patients at inclusion, 37% were categorized as having UA, and 22% were diagnosed with RA. After 1 year of follow-up, 32% of the UA patients fulfilled the ACR 1987 criteria for RA. The percentage increased to 40% at 3 years of follow-up.[14] Validation and modification of original cohorts derived in Leiden show 100% of patients with a score 8.0 had progressed to RA, whereas 94% of patients with a score 6.0 did not develop RA.[3] Further studies showed that predictors for RA development, previously used to develop the Leiden prediction rule in UA patients, are largely similar to predictors for arthritis persistency.[15] Recently, in a small pilot study in a Canadian cohort of early UA, the validation of the score revealed that 72% patients with score <5 did not develop RA and 97% with score >8 did develop RA. In India, a small sample cohort of early arthritis was followed over 3 months using Leiden prediction rule for predicting development of RA, and it showed that this rule was not validated in Indian cohorts. However, in our study, we found that Leiden prediction rule is a fast and easy tool to help identify patients with UA, who may go on to meet criteria for RA in future. Baseline scores >7 predicted those who developed RA by 12 months. From this study, it is clear that Indian patients with a predictive score of 7 or more are clearly associated with the development of RA in 100%, whereas those with a score in between 4 and 7 has a major chance of 70.6% of remission or other diagnosis at 1-year follow-up. A score of 4 or less is also clearly nullifying the possibility of future development of RA at 1 year.

These findings resemble the original model, where scores of <6 and above 8 most accurately predicted outcome. Similar to the Leiden derivation cohort, the number of tenders and swollen joints, RF positivity, anti-CCP positivity, and poor functional status predicted the development of RA. Specifically, in Indian cohorts, a value of 7 or more is associated with the outcome of RA in comparison to the Western studies. The discrimination value of the ROC curve analysis, shown by the AUC was 0.897 (SE 0.043).

In search of a more simplified prediction formula applicable to the same cohort, we have developed a formula, using only three clinical parameters from Leiden's original nine variables. ROC curve was plotted with the formula:

$$D = 0.164 \times T + 0.066 \times M + 0.012 \times A - 2.838.$$

TJC (T), duration of morning stiffness (M), and duration of arthritis (A) was 0.164, 0.066, and 0.012, respectively. The constant was calculated as −2.838.

A score of <0 means patients will not develop RA whereas a positive value means progression to RA in future follow-up. ROC curve analysis of our discriminant function, with AUC at 95% confidence interval was 0.845 (SE 0.054). In comparison, AUC of Leiden prediction score was 0.897 (SE 0.043) [Figure 1], which is very much comparable. This simpler version of prediction model may help us in developing world

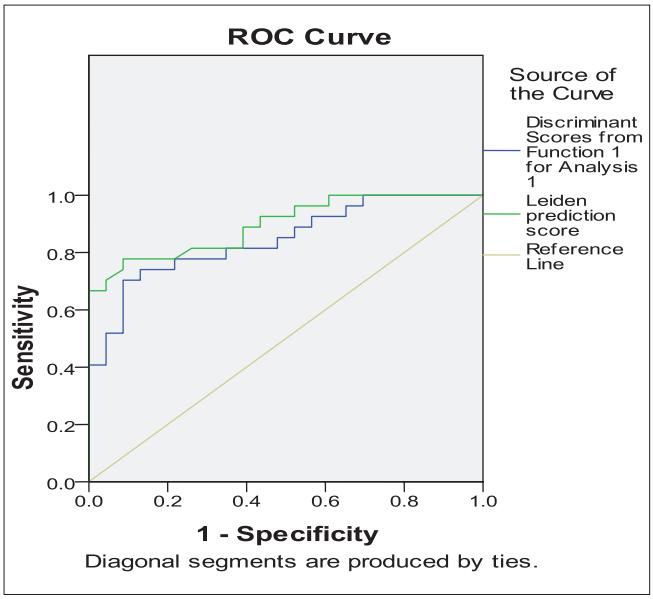

Figure 1: Area under the curve

where costly investigations always jeopardise treatment and diagnosis. However, before coming to conclusion, a large multi-center study is needed with larger cohort for both internal and external validation.

The major limitation of our study is of small sample size, and it differs from the derivation cohort of Leiden original prediction in three major ways. First, a large proportion of our patients with UA (54%) on follow-up developed RA, compared with 31% of the Leiden cohort. Later, 8% patients were found to be suffering from postviral arthritis, namely dengue and chikun gunya fever, which are common diseases in Southeast Asian countries but were not studied in Leiden. About 4% of patients were later diagnosed as SLE according to ACR criteria. A single female patient subsequently developed scleroderma whose initial presentation was very similar to early RA. These differences may reflect our inclusion criteria favoring types of inflammatory arthritis, such as RA, based on presenting signs and symptoms. In contrast, patients with any physical examination evidence of arthritis are enrolled in the Leiden clinic and, therefore, may encompass more benign forms of arthritis or even self-limiting disease. A large multi-center study involving more patients with early arthritis is needed to support this pilot study and also validate the prediction formulation we have derived.

Duration of morning stiffness at presentation was found to have significant correlation to future development of RA at 1 year though it has been excluded from recently proposed EULAR/ACR criteria of RA classification. Symptom duration at first visit to our center has a positive prediction for RA. Forty percent of our patients present after 3 months of their onset of symptoms, of these 48.1% develop RA in 1-year follow-up. This indicates that a large number of patients come to us after the loss of window of opportunity when erosive damage has already expected to have occurred.

Conclusions

Leiden score is partially valid in the Indian patients with UA and larger study is needed to validate the formulation taking only clinical variables of original Leiden prediction model.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Test result variable(s)	Area	Standard error[a]	Asymptotic significant[a]	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
Discriminant scores from function 1 for analysis 1	0.845	0.054	<0.001	0.739	0.952
Leiden prediction score	0.897	0.043	<0.001	0.813	0.981

[a]Null hypothesis: True area=0.5

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