ORIGINAL ARTICLES

The inflammatory disease burden at presentation is a good indicator of early LDA/remission: A retrospective study

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Abstract

Background: Factors predicting early response to treatment in rheumatoid arthritis (RA) assist in optimizing treatment strategies. DAS28CRP is routinely used to measure treatment response, whereas the role of associated biomarkers has not been thoroughly assessed.

Objective: To examine the clinical utility of baseline demographic, clinical, and immunological parameters as predictors of early response to treatment in RA patients. To develop an empirical equation to assess the probability of early remission.

Methods: We included data from newly diagnosed RA patients who fulfilled ACR-EULAR 2010 classification criteria in an exploratory, retrospective observational study. Patients' initial assessment and follow-up data were collected. Variables were assessed by t-test or Mann-Whitney test as appropriate, univariate regression and receiver operating characteristic (ROC) curve. A predictive equation was developed using multiple logistic regression. Model accuracy evaluated by ROC curve. The bootstrap procedure was used to assess internal validity.

Results: The study included 159 patients after screening for inclusion and exclusion criteria. A multivariate logistic regression with age, haemoglobin percentage (Hb%), neutrophil-to-lymphocyte ratio (NLR) and DASCRP was performed. The discriminatory ability of the predictive model was fair, area under the curve (AUC) = 0.711 (95% CI- 0.630-0.792) with P-value <0.001 and calibration slope of 0.98. The corresponding sensitivity and specificity noted were 49.2%, and 78.7%. The bias-corrected C index was 0.683.

Conclusion: This multivariate logistic equation improves on currently recommended methods of screening for remission. The baseline DAS28CRP score is a strong predictor and inclusion of additional factors like NLR and Hb% contribute to prediction. Further studies in a large cohort could improve and confirm these results.

Keywords: Rheumatoid arthritis, early remission, DAS28CRP, predictive equation, logistic regression

Introduction

The treatment target of rheumatoid arthritis (RA) has shifted from symptom relief to achieving low disease activity (LDA) and, if possible, remission.[1] Various studies have shown that early responders to treatment have a long-term good prognosis, independent of therapy. The speed of response thus has prognostic implications and may be useful for selecting an initial therapeutic agent or in guiding switch strategies when early response is poor.[2] The long-term follow-up of NEO-RACo trial involving 99 patients with early RA has reported that only 20% of the subjects, treated early with combination DMARDs and prednisolone, had more than one clinical features of treatment failure at 60 months. The study also concluded residual clinical disease activity at 3-6 months as the most important predictor for identifying such patients.[3] Canadian Early Arthritis Cohort (CATCH) study has suggested that the factors that may reduce the probability of sustained remission are female

sex, increased pain, and lack of initial DMARD therapy. The study also supports achieving early remission as it is related to sustainability of remission.[4] These observations suggest that factors predicting an early response to achieve LDA/remission may be effective in categorizing the poor responders and optimizing therapeutic strategies.[5-7] The recent trials on attaining LDA could improve functional and radiographic outcomes in short-term by changing the treatment in conjunction with tight control strategies.[8, 9]

The time-to-remission and chance of sustained remission are inversely related. The intensive treatment strategy may reduce the time-to-remission and leads to sustained remission, but the association between time-to-remission and sustenance of remission needs further exploration.[10] Attainment of good treatment response within the first year is reported to be independently associated with factors other than initial treatment alone.[11,12] The above observations support the fact that a generalized intensive therapeutic approach in RA patients is not justifiable. The narrow toxicity-therapeutic ratio may also expose a substantial proportion of patients to unwanted higher doses of DMARDs.[13, 14]

Delineating the factors that can predict a patient attaining LDA/remission within 3 months from the point of initiating treatment will assist in personalizing the DMARD treatment from aggressive to more simplified regimen. The present study analyzed the following factors as possible predictors of early response to DMARD to achieve the target of LDA: duration of illness, inflammatory load, and other characteristics of the diseases. Though the factors like seropositive status, genetic and other immunological components influence the outcome of LDA, it is presumed that they all lead to phenotypic expression of aggressive disease. Hence, we have focused on the easily measurable characters of disease. As a preliminary step, we undertook a retrospective chart-based study to evaluate the factors predicting the early response in treatment-naïve patients.

Materials and methods

The retrospective case-cohort study considered RA patients who visited our centre for the first time during the period December 2010 to 2011. Patients who fulfilled ACR-EULAR 2010 classification criteria were included. The exclusion criteria considered were: patients who had received biologicals or participated in clinical trials, not followed up regularly, did not comply with prescribed treatment regimen, who had taken optimum doses of DMARDs 3 months prior to presentation, whose disease assessment was inadequate, had other rheumatologic diseases, had >10yrs of duration of illness (chronic cases), and who had outlier values for variables. Patients' disease activity was recorded at initial visit and at 12±2, 24±2, 36±2 and 52±2 week visits from the day of initiating DMARD. DAS28CRP was calculated at each visit by 3 variable method and EULAR response was noted.[15] The study was approved by the institutional ethics committee. The patients were managed as in any regular clinical practice in the institution.

Clinical and biological assessment

The following demographic and clinical characteristics were extracted from the chart: age, gender, duration of illness (DOI), total joints involved (66 joints count), associated rheumatologic diseases, rheumatoid factor (RF) titer, and anti-cyclic citrullinated peptide antibody (ACCP) titer, if done. The following data were collected at initial visit and at 12±2, 24±2, 36±2 and 52±2 weeks: tender (TJC) and swollen (SJC) joint count (28 joints), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin percentage (Hb%), total leucocyte count (TLC), lymphocyte and neutrophil percentage, and neutrophil-tolymphocyte ratio (NLR).

The DAS28CRP score was calculated at each visit and the patients with the score <2.6 attained for first time were designated to have attained remission or LDA. A sustained DAS score was not essential. The patients were stratified into two groups. Subjects who never achieved a DAS score <2.6 even by the end of 3 months were classified as no remission group and those who achieved DAS score <2.6 by the end of 3 months as remission group. The patients' disease status based on whether in remission or not was taken as dependent variable.

Statistical analysis

The two groups were compared for differences in demographic, clinical, and inflammatory markers by t-test for continuous variables with normal distribution and Mann-Whitney U test for continuous variables without normal distribution. Chi-square test was performed for categorical variables. P value of ≤0.05 was considered significant. The predictors for the multivariate logistic model were selected based on univariate logistic regression cut-off P value of <0.1 and clinical logic. The selected predictors' significance in classifying the patients into outcome groups were also assessed using receiver operating characteristic (ROC) curve. To verify the influence of predictors on patients' disease status (no remission vs. remission), a

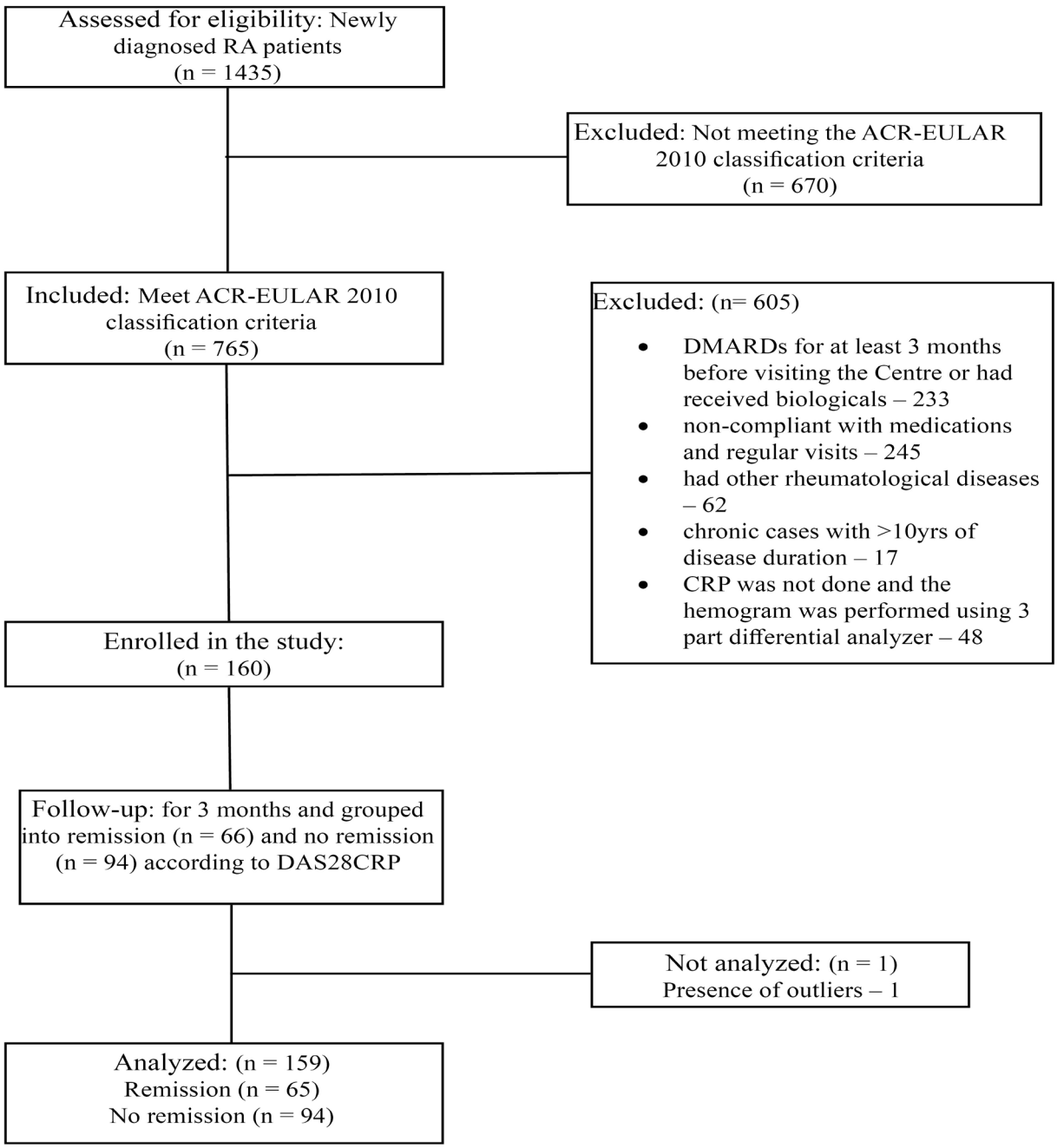
multivariate logistic regression was performed. The fit of the logistic regression model was evaluated by ROC curve and calibration slope. The internal validity of the prediction model was assessed by bootstrap method.[16] SPSS 22 and R version 3.2.2 software was used to perform the statistical analysis.

Results

The screening and enrollment of RA patients are presented as a CONSORT flow diagram (Fig. 1). A total of 159 subjects were selected for the study. Sixty-five patients who attained a DAS score of <2.6 within 3 months of therapy were classified into the remission group and 94 patients who did not achieve remission during the same period into the no remission group.

The following independent predictors were considered for the study: age, gender, DOI, RF, TJC, SJC, Hb%, TLC,

Fig. 1: CONSORT flow diagram on screening, enrollment, follow-up and analysis of subjects for prediction of early remission in RA



NLR, ESR, CRP and DASCRP. The demographic data of the two groups are given in table 1. All the patients were managed as per the routine care. The patients were managed with methotrexate, hydroxychloroquine and if the pain was severe, a depot methyl prednisolone of 160 mg was given in their initial visits prior to the initiation of DMARD treatment. Dose of methotrexate escalated to tolerable dose or maximum of 25 mg. Third DMARD combination was added generally after third month.

The Mann-Whitney U test and t-test (Table 1) showed a statistically significant difference at P ≤0.05 between the groups for age (P=0.017), DOI (P=0.033), TJC (P<0.001), SJC (P=0.004), TLC (P=0.033), ESR (P=0.046), CRP (P=0.012), and DASCRP (P<0.001). A trend towards significance was noted for Hb% (P=0.056). There were no significant differences between the groups with respect to RF, and NLR. The chi-square analysis also showed no difference with regard to the gender.

Variables selected for multivariate logistic regression to ascertain the likelihood of patients achieving remission included: age, RF, Hb%, NLR, and DASCRP. Age, Hb% and DASCRP were selected based on univariate logistic regression cut-off p value <0.1 (table 1). RF and NLR were included based on their clinical relevance as predictors in the logistic model. Though TJC, SJC and CRP were significantly different and were within cut-off P value of <0.1, they were excluded from the analysis, since DASCRP is a composite score of all three and is also used in classifying the dependent variable. TLC and ESR were excluded due to multicollinearity with other predictors. Duration of illness and gender were also excluded as the cut-off P value was not <0.1. ROC analysis of the five selected parameters showed DASCRP and age were significantly discriminating the disease outcome (Table 2).

Since the regression co-efficient value for RF was zero in the 5-variable multivariate logistic model, the variable was

Table 1: Comparison and univariate logistic regression of demographic, clinical, and inflammatory markers in RA patients

Predictors*	No remission	Remission	t-test/Mann-Whitney U test/ Chi square test#	Univariate logistic regression
	(n= 94)	(n= 65)	P value	P value
Age in years	48.5 (21-70)	43 (22-66)	0.017	0.023
DOI in months	18 (1-120)	12 (1-120)	0.033	0.092
RF	176.5 (3.92-1033)	205 (2.4-1075)	0.726	0.494
TJC	13 (1-28)	6 (0-28)	<0.001	<0.001
SJC	3 (0-24)	1 (0-21)	0.04	0.007
Hb%	11.56±1.69	12.08±1.62	0.056	0.059
NLR	2.3 (0.88-6.33)	2.12 (1.06-6.98)	0.341	0.465
TLC	8375 (4080-16990)	7860 (3590-16280)	0.033	0.06
ESR	65 (8-130)	52 (5-116)	0.046	0.045
CRP	16.5 (0.21-136)	10.3 (0.01-136)	0.012	0.015
DASCRP	4.94±1.27	4.05±1.18	<0.001	<0.001
Gender (F/M)	81/13	58/7	0.567	0.568

DOI: duration of illness, RF: rheumatoid factor, TJC: total joint count, SJC: swollen joint count, Hb%: hemoglobin percentage, NLR: neutrophil-to-lymphocyte ratio, TLC: total lymphocyte count, ESR: erythrocyte sedimentation rate, CRP: C - reactive protein, DASCRP: disease activity score-based on CRP

*Continuous variables represented as mean±sd or median(range) and categorical variables represented as counts(percentage).

Gender was analysed by chi-square test, Hb% and DASCRP by t-test and the remaining variables by Mann-Whitney U test.

Table 2: Area under the receiver operating characteristic curve of individual predictors influencing early remission in RA patients

Variables	Area under the curve	P value	95% confidence interval	
			Lower bound	Upper bound
Age	0.611	0.018	0.523	0.699
RF	0.516	0.726	0.426	0.607
Hb%	0.571	0.129	0.481	0.661
NLR	0.545	0.341	0.453	0.636
DASCRP	0.695	<0.001	0.613	0.778

RF: rheumatoid factor, Hb%: hemoglobin percentage, NLR: neutrophil-to-lymphocyte ratio, DASCRP: disease activity score-based on CRP

Table 3: Maximum likelihood estimation of the multivariate logistic regression equation for prediction of early remission in RA patients

Variables	Regression co-efficient	Standard error	Wald statistic	P value	Odds ratio	95% confidence interval
Constant	1.804	1.65	1.194	0.274		
Age	-0.024	0.015	2.516	0.113	0.976	0.95 - 1.01
Hb%	0.103	0.12	0.848	0.357	1.109	0.89 - 1.38
NLR	-0.015	0.137	0.012	0.913	0.985	0.75 - 1.29
DASCRP	-0.506	0.156	10.48	0.001	0.603	0.44 - 0.82

Hb%: hemoglobin percentage, NLR: neutrophil-to-lymphocyte ratio, DASCRP: disease activity score-based on CRP

removed from the analysis. The following final multivariate logistic model with age, Hb%, NLR and DASCRP as predictors was tested: $P= 1 + 1/(1 + e^{-X})$, where X = Constant + b_1(age) + b_2(Hb%) + b_3(NLR)+ b_4(DASCRP), where P is the probability of remission (y=1) and b_1, b_2... b_4 are the coefficients of respective explanatory variables.

The predictors were included into the model by simultaneous entry method. The Omnibus test for the full model against the constant only model was statistically significant, indicating that the predictors as a set were reliably distinguishing between remission and no remission patients, -2loglikelihood 193.110 with df (4), P <0.001. The Hosmer-Lemeshow goodness of fit test was 5.455 (P=0.708) with 8 degrees of freedom. The model explained 17.4% (Nagelkerke R^2) of the variance and classified 66.7% of cases correctly. Among the variables (Table 3), Wald criterion demonstrated that only DASCRP (P=0.002) made a significant contribution to the prediction with 95% CI, not crossing 1. Odds ratio indicated that one unit raise in DASCRP, decreases the log odds of patients attaining remission by a factor of 0.603. Age, Hb%, and NLR variables did not add significantly to the model. Interactions between the variables of any combination did not add significantly to the model and to the classification percentage, hence it was not included in the equation. The equation met the linearity assumption for logistic regression analysis.

The final prediction equation was calculated with the logistic regression parameters (Table 3), predicted probability for each case calculated: $P= 1 + 1/(1 + e^{-X})$, where X = 1.804 + (- 0.024 x age) + (0.103 x Hb%) + (- 0.015 x NLR) + (- 0.506 × DASCRP).

Based on the classification table, the corresponding sensitivity and specificity noted were 49.2% and 78.7% (Table 4). The model had positive predictive value (PPV) of 61.5% and the odds of being affected given a positive result (OAPR) of 1.6. The fit of the logistic regression model was evaluated by ROC curve (Fig. 2). The area under the curve (AUC) was 0.711 (95% CI- 0.630-0.792) with P-value <0.001, significantly different from 0.05. The effect size was small, indicating that the discrimination of the model was only fair. The calibration slope was 193.110 – 3/193.110 = 0.98. The bias-corrected C-index obtained from 1000 bootstrap samples from the original sample was

0.683, which was slightly less than the final model AUC.

Discussion

The present study clearly suggests that the baseline inflammatory load is the significant indicator of patient achieving LDA/remission in RA patients receiving routine DMARD therapy. The DMARD therapy used in the present cohort was double drug combination of methotrexate and hydroxychloroquine. The DASCRP at baseline could significantly predict patient achieving remission. As a single predictor, its predictability was 62.9%. Addition of age, NLR and Hb% increased the predictability to 66.7%. This is more than the proportional by chance accuracy rate criteria of 64.6% for the model. These additional factors, although did not reach significance, influenced the predictability considerably. The predictors as a set were significant for the full model test. RF titer, as a continuous variable, is not a good predictor; but grouping them into high and low titers could improve the model fit. The NLR and Hb% are influenced by inflammation. Literature evidence clearly indicates that low Hb% and the NLR reflects the presence of chronic inflammation.[17-21] Thus it could be concluded that age and intensity of inflammation influence the attainment of early remission in RA patients.

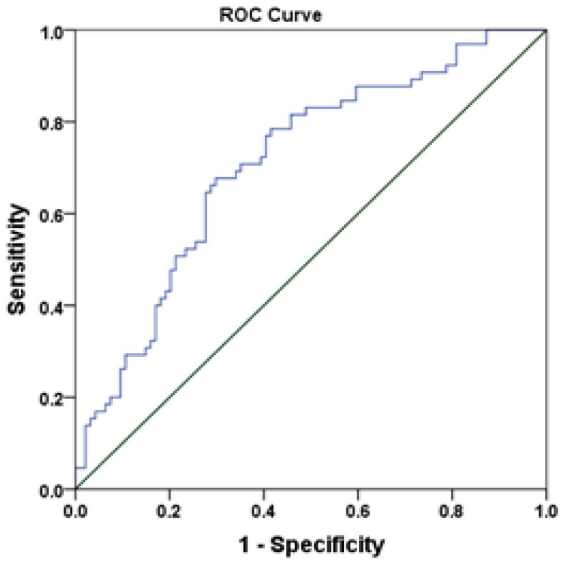
There are adequate studies suggesting similar findings. Some of the recently published studies report that the presence of LDA indicates a better response.[22] Another study has demonstrated that increased age, low functional status, and concomitant prednisolone treatment are negative predictors for ACR70 treatment response.[23] Factors like functional status and need for steroid are

Table 4: Subjects screened by different predictors for early remission in RA patients

Variables in the model	Number of true positives	Number of false positives	Number of false negatives	Number of true negatives	Sensitivity	Specificity
DASCRP	27	21	38	73	41.50%	77.70%
Age, Hb%, NLR, & DASCRP	32	20	33	74	49.20%	78.70%

Hb%: hemoglobin percentage, NLR: neutrophil-to-lymphocyte ratio, DASCRP: disease activity score-based on CRP

Fig. 2: ROC plot evaluating the fit of the logistic regression model for early remission in RA patients



ROC discriminates between prediction probability and observed outcome. A larger area under the curve indicates better perfomance of the predictive equation

influenced by high disease activity. In a treat-to-target study, early RA patients with symmetrical joint involvement, anti-CCP positivity and fewer tender joints at baseline achieved satisfactory improvement in pain after 6 months of treatment.[24] This concurs with findings of both randomized control trial (TEMPO) and clinical practice setting (RADIUS II) studies, suggesting that patients with LDA are more likely to attain early remission. The probability of continued remission is more likely in patients who achieved earlier remission.[25]

According to the large real-life CORRONA study, men are more likely to achieve sustained remission compared to women in early RA.[26] The study had used ESR-based remission criteria. The reason for no gender influence on the early remission outcome in the current study could be due to the use of CRP-based remission criteria. Even our previous studies on remission criteria has suggested that patients gender influences differently in achieving ESR and CRP based remission.[27] Yanez *et al.* have observed that recent-onset RA patients with younger age and LDA achieved earlier sustained remission upon treatment.[28]

The RF or anti-CCP has been identified as a prognostic factor for RA, but the reports are inconsistent. There is no adequate well-designed study to suggest RF IgG, IgA, and IgM as good predictors. An observational study has reported that baseline IgM RF titer is not a good predictor of response to TNF antagonists in RA. However, the inclusion of heterogeneous studies for the meta-analysis hampered the generalizability of the study findings.[29] The study by Sakthiswary *et al.* have found that only IgA RF and anti-CCP levels were significantly high in the non-responder group when compared to the responders and controls (P = 0.001, P = 0.034, respectively). In the same study, only the IgA RF remained significant (OR 0.989; 95% CI 0.980-0.999; P = 0.026) in multivariate analysis, suggesting pre-treatment IgA RF levels as a serological predictor of poor response to tumor necrosis factor α inhibitors in RA.[30] The present study shows that RF has least discriminative power between non-responsive and responsive groups. It is worth considering RF as one of the prognostic classification variable, since it is an indicator of more aggressive disease. Moreover, inclusion of RF as a stratified variable with low, moderately high, and high titer could improve its discriminative ability. We are planning to evaluate it in a much larger prospective study.

There are studies highlighting the importance of early response in predicting the likelihood of fundamental disease suppression, including protection from structural damage. Early initiation of treatment in RA assists patients in attaining improved outcomes and drug-free remission by profoundly modifying the pathogenesis of RA.[31-34] RA patients on early DMARDs show a significantly lower disease progression rate, irrespective of the differences in treatment regimen or disease characteristics.[35-37] Studies have also shown that early intervention group had significantly lower radiographic damage at 5 years.[38] However, the present study suggests that the influence of duration of illness on patient attaining DAS score <2.6 at the end of 3 months was not significantly different.

In the current study, the sensitivity and specificity of the predictive equation were 49.2% and 78.7%, respectively. The use of sensitivity and specificity in clinical decision making is based on classifying false negatives (remission identified as no remission) and false positives (no remission identified as remission). The high specificity of the predictive model indicates minimal false positives and its ability to correctly identify no remission cases. Having increased false positives may cause the false identification of patient not in remission as on remission. Discontinuation of intensive therapy based on such false predications may lead to disease progression.

A test with low sensitivity will produce a large number of false negatives. The present model has low sensitivity, thereby increasing the number of missing cases on clinical remission. Such incorrect classification of patients as not attained remission may lead to continuation of intensive therapy. When only DASCRP is used, the number of false negatives were 38 out of 65 subjects (58.46%) who attained remission and false positives were 21 (Table 4). Whereas in the present model, the number of false negative cases were 33 out of 65 cases (50.77%) and false positives were 20. The current model has reduced the false negatives, while it has maintained the number of false positives cases. Such false negative cases could be identified during follow-up visits, and continuation of intensive therapy is not associated with complications in short term. The predictive model provided a PPV of 61.5% and an OAPR of 1.6. The former indicates that, among those predicted as having remission by the model, 61.5% were actually on remission. Whereas the latter shows that the odds of having a true-positive test result are 1.6 times greater than the odds of having a false-positive result. OAPR <1 identify fewer true positives than false positives.

The overall performance of the prediction model is fair (AUC=0.711), yet the model can be used. The bootstrap c index had AUC=0.683, a slight decrease from the multivariate model, suggesting a small degree of over-fitting in the original model. The bias-corrected c-index and calibration slope of 0.98 (~1) indicates a well-calibrated model. Thus, it could be concluded that the best predictor of an early response is the disease activity, as measured by DASCRP, and supported by age, NLR and Hb%. The predictive implications of the present pilot study are confined to the study population. External validation of a prediction model is required for its general applicability. Validation involving multi-centre participation is mandatory for predicting remission and to confirm the optimum risk threshold for individual variables. The predictive equation requires adjustment for different variable ranges due to the heterogeneity in population. The current findings would require prospective validation in different populations. Inclusion of additional markers could increase the predictability. The study is a retrospective cohort and the treatment regimen was not within the controlled environment. This may have added bias, though literature has suggested that treatment does not influence outcome as long as they are uniform. Addition of RF was not possible because the sample size was not sufficient for its inclusion as a stratified variable.

Early prediction of patients' risk of disease progression based on more objective measures, in addition to DASCRP, may augment clinical judgement. We have attempted to define sub-sets of RA patients who responded to specific treatments, using readily available clinical and laboratory data. An alternate therapeutic strategy, with a combination of DMARD and/or biologicals, could be introduced for treatment of non-responders.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Citation

Chandrashekara S, Utkarsha CN, Anupama KR. The inflammatory disease burden at presentation is a good indicator of early LDA/remission: A retrospective study. IJRCI. 2016;5(1):OA2.

Acknowledgement

We acknowledge the help of www.research-assist.com for editing the manuscript and The Immunology and Arthritis Research and Education trust (IARET), Bangalore, an independent trust supporting research in arthritis and education, for funding the study.

Submitted: 6 October 2016, **Accepted: 7** February 2017, **Published:** 13 March 2017

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