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## SHORT COMMUNICATION

# Raising Rheumatoid Factor Cutoff Helps Distinguish Rheumatoid Arthritis

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**SUMMARY** The presence of rheumatoid factor (RF) is one of the clinical criteria for the diagnosis of rheumatoid arthritis (RA). The cutoff point of RF assays is usually based on a reference level obtained from normal subjects in the same population as the patients. We evaluated 63 rheumatoid arthritis (RA), 25 other arthritis patients and 110 blood donors. Their rheumatoid factors (RF) ranged from < 9.9 to 2,264, < 9.9 to 262, and < 9.9 to 66 mIU/ml, respectively. The sensitivity at different cutoff points of 15, 20, and 25 mIU/ml was 92.1%, 90.5%, and 88.9%, respectively. The specificity at the same cutoff points was 81.5%, 84.4%, and 85.2%, respectively. Having minimally sacrificed the sensitivity, we recommend using a higher RF cutoff to increase specificity.

Rheumatoid arthritis (RA) is an autoimmune arthropathic disease diagnosed by having 4 of 7 specific clinical criteria.[1] One of the criteria is the presence of serum rheumatoid factor (RF). The RF has been traditionally detected by hemagglutination or latex agglutination.[2] Recently, a nephelometric analyser has been utilized with the advantage of a quantifiable result.[3] It is recommended that each laboratory should establish its own cutoff point for the population served. The purpose of this study was to determine the best cutoff level for quantitative RF assays for the Thai population.

## MATERIALS AND METHODS

### Cases

RF results of patients' sera sent for routine RF testing to the Clinical Immunology Laboratory, Ramathibodi Hospital, Bangkok, Thailand, from 15 December 2000 to 15 January 2001 were reviewed for the study. Medical records of 108 cases were available for reviewing. Among them, only 88 cases had enough information for evaluation and 63 RA cases (6 males and 57 females, aged 22-72 years, mean age 44.1), were identified using the 1988 Revised American Rheumatism Association (ARA) Criteria for the Classification of Rheumatoid Arthritis.[1] The other 25 patients were grouped as non-RA cases (4 males and 21 females, aged 23-80 yrs, mean age 50) consisting of 15 cases with osteoarthritis or arthralgia, and 10 cases with other connective tissue diseases. Sera from 110 blood donors were also recruited as control group.

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**RF detection**

Sera were tested by an RF latex reagent kit (N Latex RF, Dade Behring, Germany) using an immunonephelometrical autoanalyser (Enphelometry 100, Dade Behring, Germany) according to the manufacturer's instruction. The measured test range was 10-600 mIU/ml. Sera with the titers over 600 mIU/ml were further diluted and retested.

**Statistical methods**

Sensitivity and specificity for each cutoff point were determined using Analyse-it Clinical Laboratory 1.71 (Analyse-it Software, Leeds, UK) for the data analysis. Receiver operating characteristic (ROC) analysis was generated. The area under the ROC curve and the standard error (S.E.) were calculated by Wilcoxon's non-parametric method.[4]

## RESULTS

Among the 63 RA patients, 5 cases had RF below the detection limit (< 9.9 mIU/ml) and 58 cases had RF ranging from 15.1 to 2,264 mIU/ml. Among the 25 non-RA patients, 4 cases had RF < 9.9 mIU/ml and 21 cases had RF ranging from 15.1 to 1,449 mIU/ml. In the healthy group, 105 blood donors had RF < 9.9 mIU/ml and 5 donors had RF levels at 14.8, 17.8, 60.1, 62.8, and 147.5 mIU/ml. The distribution of RF levels in each group is shown in Fig. 1A.

Sensitivity and specificity of the RF test at cutoff points of 10 to 40 mIU/ml are shown in Table 1. The sensitivity was 92.1% at a cutoff level of 15 mIU/ml as recommended by the manufacturer, and decreased to 90.5% and 88.9% at 20 and 25 mIU/ml, respectively. The specificity was calculated separately using the blood donors, non-RA patients, and non-RA patients plus blood donors, as control groups. The specificity of the non-RA group was 16% to 44% at cutoff 15 to 44 mIU/ml. On the other hand, specificity of the blood donors was at 96.4% to 97.3% at cutoff 15 to 44 mIU/ml. The specificity of the combined blood donors and non-RA groups increased from 81.5% to 84.4% and 85.2%, when the cutoff was raised from 15 to 20 and 25 mIU/ml, respectively.

To determine whether the RF possessed diagnostic value, a ROC curve was generated by calculating sensitivity and specificity from all possible cutoff points of the set using non-RA patients plus

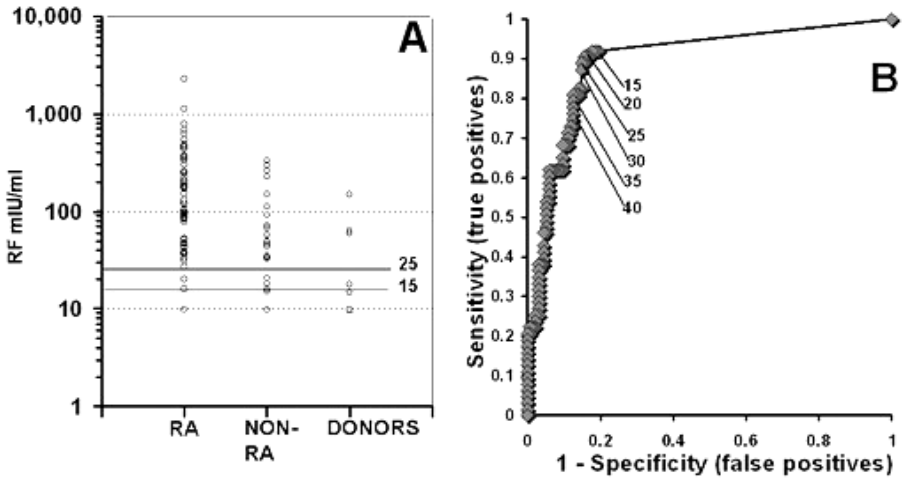


**Fig. 1** A, Distribution of rheumatoid factor levels in rheumatoid arthritis (RA), non-RA, and blood donors groups (log scale). The 15 and 25 mIU/ml cutoff lines are shown. B, ROC curve (sensitivity against false positive rate at each possible cutoff point) of the rheumatoid factor test. Non-RA and blood donors were used as control. Area under the curve 0.897, S.E. = 0.0255 (95% confidence interval, 0.847-0.947), $p < 0.0001$. The cutoff points of 15, 20, 25, 30, 35, and 40 mIU/ml are marked.

**Table 1** Sensitivity and specificity of the RF at cutoff 10-40 mIU/ml

| RF cutoff (mIU/ml) | Sensitivity | Specificity (blood donors) | Specificity (non-RA) | Specificity (non-RA and blood donors) |
|---|---|---|---|---|
| **10** | 92.1% | 95.5% | 16.0% | 80.7% |
| **15** | 92.1% | 96.4% | 16.0% | 81.5% |
| **20** | 90.5% | 97.3% | 28.0% | 84.4% |
| **25** | 88.9% | 97.3% | 32.0% | 85.2% |
| **30** | 87.3% | 97.3% | 32.0% | 85.2% |
| **35** | 81.0% | 97.3% | 44.0% | 87.4% |
| **40** | 76.2% | 97.3% | 44.0% | 87.4% |

blood donors as control group (Fig. 1B). The area under the ROC curve was 0.897 ($p < 0.0001$) denoting the RF having diagnostic value.[4]

## DISCUSSION

Using sera from both RA and non-RA groups as well as healthy blood donors, this study evaluated a quantitative RF test at all its possible cutoff points. The RF levels in both RA and non-RA groups covered a wide range. As a result, high cutoff points in the non-RA group adversely affected the specificity, while low cutoff points in the RA group adversely affected the sensitivity.

Another study using patients admitted to the rheumatology department had reported a high specificity of 95.9% at 19 mIU/ml cutoff.[3] In contrast, the non-RA group in this study being not only recruited by rheumatology specialists but also by primary care physicians had a lower specificity at 20 mIU/ml cutoff (Table 1). A different study including a variety of diseases in the non-RA group similar to this study also exhibited a specificity of only 89.6%.[5] Nevertheless, the data of the Thai population in this study showed a higher non-specificity of the RF test than other reports. The healthy population represented by the blood donors in this study had 2.7% (3 of 110) of RF > 20 mIU/ml, in contrast to only 0.02% in another study in Finland.[6]

Being positive in various conditions, the RF test was criticized for its lack of specificity and raising the cutoff was recommended to make the test more specific.[3]

However, the strategy of raising the cutoff was thwarted by a reduction in sensitivity (Table 1). Most of the quantitative RF tests using the immunonephelometric technique set the cutoff at 15 mIU/ml . However, as the RF is part of the ARA criteria for a clinical diagnosis,[7] the emphasis should be on specificity. If the blood donor group was used alone to calculate specificity, it exhibited only minimal change across various cutoff points. The inclusion of non-RA patients in the control group was to reflect the situation of using RF in clinical practice. This study demonstrated that a slightly higher cutoff of 20 or 25 mIU/ml could increase specificity considerably while only minimally sacrificing sensitivity. In addition, antibody to cyclic citrullinated peptide (anti-CCP) was established as another diagnostic tool for RA.[8] This combination of new technology and a higher cutoff point for RF are valuable for the more accurate diagnosis of RA.

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