*Review Article*

# Rheumatoid Factors: Clinical Applications

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Rheumatoid factors are antibodies directed against the Fc region of immunoglobulin G. First detected in patients with rheumatoid
arthritis 70 years ago, they can also be found in patients with other autoimmune and nonautoimmune conditions, as well as in
healthy subjects. Rheumatoid factors form part of the workup for the differential diagnosis of arthropathies. In clinical practice,
it is recommended to measure anti-cyclic citrullinated peptide antibodies and rheumatoid factors together because anti-cyclic
citrullinated peptide antibodies alone are only moderately sensitive, and the combination of the two markers improves diagnostic
accuracy, especially in the case of early rheumatoid arthritis. Furthermore, different rheumatoid factor isotypes alone or in
combination can be helpful when managing rheumatoid arthritis patients, from the time of diagnosis until deciding on the choice
of therapeutic strategy.

## 1. Introduction

Rheumatoid factors (RFs), a class of immunoglobulins (Igs) that have different isotypes and affinities, were first detected more than 70 years ago, but there is still much to discover about the mechanisms underlying their production, physiological role, and pathological effects [1].

Waaler described an antibody directed against serum gamma-globulins that promoted the agglutination of sheep red blood cells sensitised by subagglutinating doses of rabbit antibodies in 1940 [2], although it had actually been previously found in patients with liver cirrhosis and chronic bronchitis by Kurt Meyer in 1922. In 1948, Rose described these antibodies in patients with rheumatoid arthritis (RA) [3], and in 1952 they were finally christened RFs because of their association with RA [4].

However, although they owe their name to their first detection in RA patients, RFs are found in patients with other autoimmune and nonautoimmune diseases, as well as in healthy subjects.

The aim of this review is to describe the clinical applications of testing for RFs.

## 2. Methods of Detection

Classic agglutination techniques were initially used because of the ability of IgMs to induce agglutination. The first RF detection assay was based on the fact that RF agglutinates sheep red blood cells sensitised with rabbit IgGs (i.e., the classic Waaler-Rose test) [2, 3], and this was followed by the development of other IgG carriers such as bentonite [5, 6] and latex particles [7, 8].

Automated techniques such as nephelometry and enzyme-linked immunosorbent assays gradually replaced the other semiquantitative methods because of their simplicity and greater reproducibility [9–12].

Multiplexed immunoassaying is an emerging high-throughput technique for the quantitative detection of multiple analytes from a single biological sample [13]. Although

they have yet to be standardised and validated, multiplexed immunoassays can reduce analytical time and enhance accuracy. However, it is known that RFs can interfere with a number of laboratory immunoassays and lead to false positive results: for example, in patients with high RF levels, the analysis of vancomycin can be compromised if serum rather than plasma samples are used [14, 15].

RFs can also interfere with other laboratory tests, including those designed to detect anticardiolipin antibodies (especially if IgM levels are in the low positive range) [16], anti-$\beta$2GPI antibodies [17], anti-HCV antibodies [18], antirubella antibodies [19], thyroid assays [20, 21], and tests for carbohydrate antigen 19–9 [22] and various cytokines [23].

## 3. Rheumatoid Factors in Nonrheumatic Conditions

As shown in Table 1, RFs can be detected in patients with many nonrheumatic conditions. Infections and chronic diseases may be characterised by the presence of serum RFs, but unlike those detected in RA patients, the RFs produced during infections are usually transient and not detrimental. Given the ability of RFs to increase the clearance of immune complexes and the fact that RF-producing B cells may behave as antigen-presenting cells (APCs) and aid the immune response against the infectious antigens, it is likely that the net impact of RF production during infections is protective for the host [24, 26].

These natural RFs are generally low-affinity, polyreactive IgM antibodies produced by CD5-positive B cells [27, 28], and coexistence of RF-positive B cells and nonautoimmune IgG antigen in healthy subjects suggests the existence of tolerance mechanisms [26].

RFs can be found in 40–50% of patients with HCV infection, but their frequency can reach 76% [29]. Their production is probably due to chronic stimulation of the immune system by HCV, and, as HCV infection is highly prevalent in various countries (1.5–3% in southern Europe) and represents the first cause of increased serum RFs, HCV antibodies should be sought in all subjects with increased RF levels [29, 30] (Figure 1).

## 4. RFs in Healthy Subjects

RF positivity has also been reported in the healthy population [31–33], and up to 4% of young Caucasians may be RF positive, with a similar distribution between the two genders. It is thought that genetic and environmental factors are responsible for the worldwide variability in distribution of RFs: for example, their highest prevalence (up to 30%) has been observed in North American Indians tribes [34–36]. The RFs found in healthy subjects are different from those present in RA patients as their titres are low/moderate and they are likely to be produced by CD5-expressing B cells as low-affinity, poly-reactive IgMs without any signs of maturation affinity [31]. The transient production of low-affinity IgM RFs may be induced by polyclonal B cell activators such as bacterial lipopolysaccharides and Epstein-Barr virus [28, 37],

TABLE 1: Rheumatoid factor frequency in different diseases and conditions.

| Disease | Frequency, % |
| --- | --- |
| Arthritis | |
|    Rheumatoid arthritis | 70–90 |
|    Juvenile idiopahtic arthritis | 5 |
|    Psoriatic arthritis | <15 |
|    Reactive arthritis | <5 |
| Other connective tissue diseases | |
|    Primary Sjögren's syndrome | 75–95 |
|    Mixed connective tissue disease | 50–60 |
|    Systemic lupus erythematosus | 15–35 |
|    Systemic sclerosis | 20–30 |
|    Dermato-/polymyositis | 20 |
|    Systemic vasculitides (panarteritis nodosa, Wegener's granulomatosis) | 5–20 |
| Infectious diseases | |
|    Bacterial infections | |
|       Subacute bacterial endocarditis | 40 |
|       Chlamydia pneumoniae infection | |
|       Klebsiella pneumoniae infection | |
|       Syphilis primary-tertiary | 8–37 |
|       Tuberculosis | 15 |
|    Viral infections | |
|       Coxsackie B virus infection | 15 |
|       Dengue virus infection | 10 |
|       EBV and CMV infections | 20 |
|       Hepatitis A, B and C virus infection | 25 |
|       HCV infection | 40–76 |
|       Herpes virus infection | 10–15 |
|       HIV infection | 10–20 |
|       Measles | 8–15 |
|       Parvovirus infection | 10 |
|       Rubella | 15 |
|    Parasitic | |
|       Chagas | 15–25 |
|       Malaria | 15–18 |
|       Onchocerciasis | 10 |
|       Toxoplasmosis | 10–12 |
| Other diseases | |
|    Mixed cryoglobulinemia type II | 100* |
|    Liver cirrhosis | 25 |
|    Primary biliary cirrhosis | 45–70 |
|    Malignancy | 5–25 |
|    After multiple immunisations | 10–15 |
|    Chronic sarcoidosis | 5–30 |
| Healthy 50-year olds | 5 |
| Healthy 70-year olds | 10–25 |

*Monoclonal IgM rheumatoid factors; CMV: cytomegalovirus; EBV: Epstein-Barr virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus. Adapted from [24, 25].
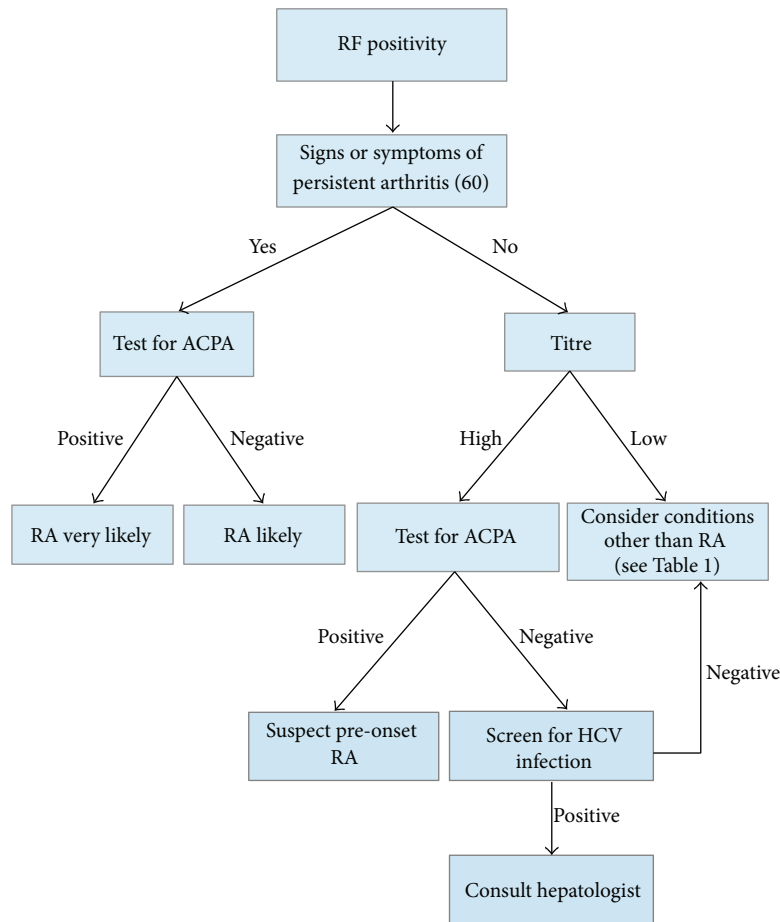
FIGURE 1: Proposed decision-making algorithm for patients who are rheumatoid factor positive at the first evaluation. RF: rheumatoid factor; RA: rheumatoid arthritis; ACPA: anti-cyclic citrullinated protein/peptide antibody.

but it has been shown that high RF titres in healthy subjects predict the development of RA [38]. Furthermore, IgM RFs are sometimes observed in healthy elderly people, which suggests that they may be a consequence of the age-related immune deregulation (Figure 1) [39, 40].

## 5. RFs in Patients with Autoimmune Diseases

RFs are frequently detected in patients with systemic autoimmune diseases, such as systemic lupus erythematosus, mixed connective tissue disease, polymyositis, and dermatomyositis (Table 1) [24, 25].

Patients with Sjogren's syndrome (SS) [41] and those with type II and III mixed cryoglobulinemia (usually HCV related) [42] have the highest RF titres.

About 60% of the patients with primary SS are RF positive, with males having higher IgA RF levels than females [41]. It is also thought that the disease-related transformation of activated RF-positive B cell clones is involved in the pathogenesis of the lymphoproliferative disorders that develop in about 5% of SS patients [43]. Most SS patients have high titres of polyclonal RFs, whereas monoclonal RFs can be

detected in patients with type II mixed cryoglobulinemia and, to a lesser extent, in SS patients with lymphoproliferative disorders [24, 34].

## 6. RFs and Rheumatoid Arthritis

Although RFs can be detected in patients with other connective tissue diseases, RF isotypes are helpful in the management of RA patients from the time of diagnosis until deciding on the choice of therapeutic strategy (Figures 1 and 2) [44, 45]. RF testing in RA patients has a sensitivity of 60% to 90% and a specificity of 85% [46, 47].

A number of hypotheses have been postulated in order to explain the possible key role of RFs in RA, including their capacity to increase the elimination of immune complexes by macrophages [48], the improved cytotoxicity of antiviral antibodies [49], and the increased elimination of parasites [1]. It has also been suggested that RFs potentiate the presentation of antigens to T cells by means of the dendritic cell uptake of immune complexes with exogenous antigens and by means of RF B cells, which seem to be more efficient APCs than other B cells [50] (Figure 3). Finally, it is possible that the rapid
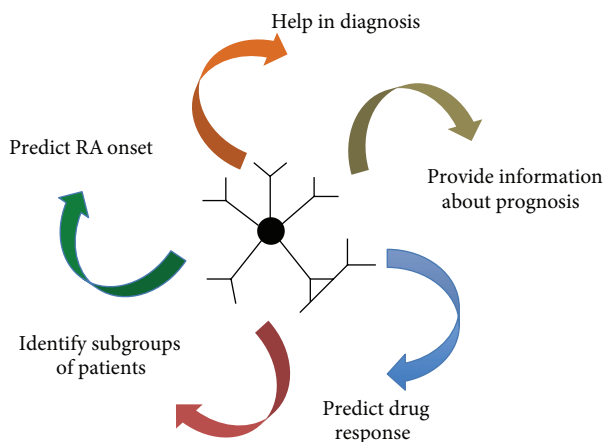
FIGURE 2: Role of rheumatoid factors in the management of rheumatoid arthritis patients.

secretion of large amounts of low-affinity RFs prevents the activation of higher-affinity RF B cells and additional B cells [51–53].

Defining RFs as anti-IgG or anti-gamma-globulins is inaccurate because it restricts RF reactivity to the IgG Fc fragment. IgM RFs are the most frequently detected isotype, but IgG, IgA, IgE, and IgD RFs can also be observed [54].

It has been shown that three RF isotypes (IgM, IgA, and IgG) are detected in up to 52% of RA patients but in fewer than 5% of patients with other connective tissue diseases. Moreover, the presence of IgA and IgG RF isotypes in absence of IgM-RF is more prevalent in patients with connective tissue diseases than in RA patients, whereas an increase in both IgM and IgA RFs is almost exclusively observed in patients with RA [55, 56]. IgM-RF specificity increases considerably at high titres [57].

*6.1. The Role of RFs in the Diagnosis of Rheumatoid Arthritis.* It has long been recognised that RFs play a pivotal role in the differential diagnosis of polyarthritis because they make it possible to identify RA patients [58]. For this reason, RF testing has been one of the classification criteria for RA since 1987 [59] and, although many years have passed since their identification, their crucial role in classifying RA has been confirmed by the updated criteria [60].

However, in order to increase the specificity of the latest RA classification criteria, anti-cyclic citrullinated protein/peptide antibody (ACPA) testing has been added. A meta-analysis [46] has shown that the pooled sensitivities of ACPA and RF are similar, but ACPA positivity is more specific for RA than IgM RF, IgG RF, or IgA RF positivity [61] and more specific for early RA than IgM RF [62]. On the other hand, sensitivity is reduced because positivity for both ACPA and RF is a more stringent criterion than positivity for either alone [46]; combining ACPA and RF positivity is more permissive in terms of sensitivity because the antibodies complement each other, especially for early RA [63–66].

Furthermore, although the cut-off value of each commercial kit is slightly different, it has been suggested that the best
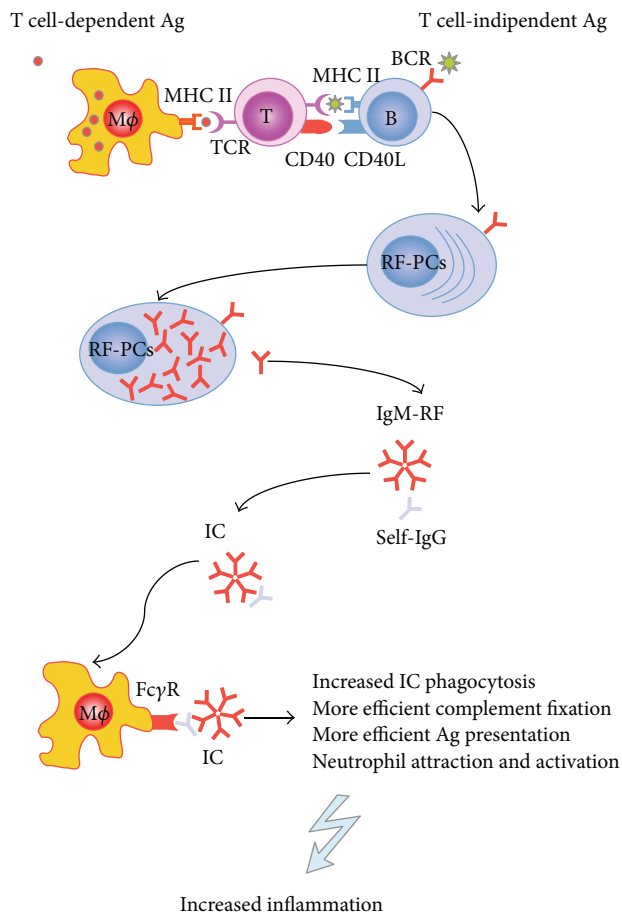


FIGURE 3: The immunological role of rheumatoid factors (RFs) in rheumatoid arthritis. RFs may be produced both in a T cell-dependent or T cell-independent pathway. Macrophages and B cells may act as antigen-presenting cells and efficiently present antigens to T cells. Ag: antigen; BCR: B cell receptor; TCR: T cell receptor; RF-PCs: rheumatoid factor plasma cells; IC: immune complex.

ACPA cut-off value should be $\geq 40$ U/mL, which leads to a positive likelihood ratio of 5.49 and a negative likelihood ratio of 0.50 [46, 67].

It has also been shown that RFs are useful in predicting the development of RA, as the detection of IgM, IgA, and IgG RFs may predate its onset by years [38, 68], and it has been reported that their appearance in serum is sequential before diagnosis: first IgM RF, then IgA RF, and finally IgG RF [57, 69].

*6.2. Prognostic and Therapeutic Relevance in Rheumatoid Arthritis.* The detection of IgM RFs is also helpful as a prognostic index, and some studies have shown that immunosuppressive treatment can decrease serum RF levels. However, the clinical usefulness of RFs in monitoring disease activity [70] and treatment response is limited [71].

It has been shown that a progressive decrease in the RF levels parallels the decrease of clinical activity in patients treated with traditional disease modifying antirheumatic drugs [72] or biologic agents such as infliximab [73–75],

etanercept [76], adalimumab [77], rituximab [78, 79], and abatacept or tocilizumab [80, 81].

There are conflicting published data concerning the potential role of RFs in predicting responses to antitumor necrosis factor alpha (TNF-$\alpha$): some studies have found that RF positivity before therapy is insufficient to predict a response [82–85], whereas others have found that it predicts a negative response [86, 87]. In particular, it has been reported that high pretreatment levels of IgA RF are associated with a poor clinical response to TNF-$\alpha$ inhibitors [88].

High serum levels of RF are predictors of more severe disease forms and B cell-depleting therapy can have a beneficial effect: RF-positive RA patients have a better response to rituximab than those who are RF negative [89–92].

## 7. Conclusions

It has been demonstrated that low-affinity RFs appear to be key player in immune responses to many infectious organisms, and high-affinity RFs indicate more severe and persistent disease in patients with RA. RFs are probably the result of the immune response to inflammation (depending on genetic background) and may have regulatory effects on Ig production by controlling B cell activation.

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