SPECIAL ARTICLE

The Rheumatoid Factor: An Analysis of Clinical Utility

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The rheumatoid factor (RF) is a frequently ordered diagnostic test, yet it possesses significant limitations in sensitivity, specificity, and predictive value. Recognition of these limitations could improve the test's utility by encouraging more selective test ordering and more circumspect interpretation of test results. An analysis of 563 requests for RF from a teaching hospital revealed a positive predictive value of only 24% to 34%. The RF performs best under conditions of moderate pretest likelihood of rheumatoid arthritis, and otherwise has rather limited clinical utility.

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Since Waaler's and Rose's earliest descriptions of the agglutination reaction eventually termed the rheumatoid factor (RF) [1], it has become one of the most frequently ordered tests in the evaluation of patients with musculoskeletal complaints. Yet, in the individual patient with a positive RF, the implications are far from clear. It may be a marker of severe, systemic rheumatic disease (most notably rheumatoid arthritis [RA]), an epiphenomenon associated with a nonrheumatic illness, or a benign coincidence of aging. Even for the patient with RA, the degree of understanding has progressed little since Ragan [2], one of Rose's co-workers, wrote in 1949:

> "It has been our impression for many years that a positive test for agglutination of group A hemolytic streptococci in the serum of a patient with rheumatoid arthritis was of poor prognostic significance.... This correlation is far from absolute, for some patients with a positive agglutination do well and some with a negative agglutination end badly."

The purpose of this article is to identify circumstances in which RF has the highest utility and those in which its yield is low, based on the best available data.

At first glance, RF appears to be a particularly useful diagnostic test: it is reportedly present in 70% to 90% of patients with RA [3–5], and it is included among the original and revised criteria for the classification of RA as accepted by the American College of Rheumatology (formerly the American Rheumatism Association) [6,7]. However, the specific characteristics of this test and the circumstances under which it is ordered affect its utility. For example, arthralgia and arthritis are common disorders, leading 15% of the American population to seek medical care or restrict activity each year. This probably contributes to the frequency with which the RF is ordered. False-positive RF test results occur in a significant proportion of total tests ordered [8–10]; thus, there are many RF-positive patients with arthralgia but without identifiable rheumatic illness. They represent an important source of confusion and potentially inappropriate diagnosis and treatment.

Further complicating the interpretation of the RF is the sizable subset of patients with RA who are RF-negative and the occasional patient with a seronegative polyarthritis (such as a spondyloarthro-

pathy or polyarticular crystal-induced disease) that is clinically indistinguishable from seronegative RA at initial presentation. The clinical usefulness of the RF is therefore driven in large part by clinicians' ordering behavior and ability to interpret test results in light of the clinical context.

DETECTION OF RF

The RF used in clinical practice is an IgM antibody directed against IgG. It has traditionally been detected by agglutination with sheep red blood cells (RF cross-reacts with IgG from other species) or latex particles attached to human IgG [11]. Results are expressed in antibody titers as the dilution required to eliminate reactivity. More recently, radioimmunoassays, enzyme-linked immunosorbent assays, or nephelometric techniques have been utilized, with the purported advantages of quantifiable results, and improved sensitivity, specificity, and reliability [12–14]. Not all reports find such advantages [15]. "Hidden" IgM, RF detected by assays other than traditional agglutination tests, or RF of an IgG, IgA, or IgE isotype is said to be present in some otherwise seronegative patients with RA [12,16,17]. However, assays for hidden RFs are not readily available and their clinical significance is unclear.

The biologic function of RF is unknown. It is present most often in RA, the elderly (usually in low titer), a number of rheumatic diseases other than RA, and neoplastic and infectious diseases (see below). The common theme among these disorders appears to be chronic antigenic stimulation, such as might be expected in infective endocarditis or chronic active hepatitis. Speculation regarding the pathogenesis of RF includes polyclonal B-cell activation by a known or unknown antigen, or dysfunction in T-cell regulation leading to B-cell production of RF [16,18,19]. Recent reviews explore the pathogenesis and biologic activity of the RF [16,20,21].

SENSITIVITY, SPECIFICITY, AND PREDICTIVE VALUE OF RF

Several elements contribute to the diagnostic utility of a test (such as the RF): sensitivity (true-positive rate), specificity (1 − false-positive rate), and positive or negative predictive value (the likelihood of disease or nondisease based on a positive or negative test result). Sensitivity and specificity are independent of disease prevalence, while predictive value is markedly affected by disease prevalence [22]. The prevalence of RA in the United States is estimated at 0.5% to 3% [8,23–25], although age (peak onset is ages 35 to 45), gender (RA is approximately three times more likely in women than in men), and family history, among other factors, affect the likelihood for an individual. The clinician's estimated likelihood that RA is present (the pretest probability of disease) determines in large part the RF's ability to aid in diagnosis. For example, if one were to use the RF as a screening test, assuming a 1% pretest probability of RA, a test sensitivity of 80%, and a specificity of 95%, the positive predictive value of the RF is 16%. Based on disease prevalence and test characteristics alone, this means that there is less than a 1 in 5 chance in a screening program that an individual with a positive RF will have RA. If instead, the clinician believes the pretest probability of RA is 15% (as might be the case in a 30-year-old woman with persistent polyarthralgia and a positive family history of RA), a positive RF increases the probability to 74% (**Table I**). Although the diagnosis of RA cannot be made on the basis of the RF alone, such examples demonstrate how the selection of patients in whom the test is ordered matters as much as (or perhaps more than) the characteristics of the particular test.

TABLE I

Post-Test Probabilities of Rheumatoid Arthritis Based on Pretest Probabilities and RF Result, Assuming That the Sensitivity of RF Is 80% and Specificity Is 95%

Pretest Probability	Post-Test Probability, RF-Positive	Post-Test Probability, RF-Negative
1%*	16%	0.2%
15%	74%	4%
25%	84%	7%
50%	94%	17%
75%	98%	39%
90%	99%	65%

*The estimated prevalence of RA in the United States is 0.5% to 3% [8,23–25].

In most clinical laboratories, the RF, by definition, is positive in no more than 5% of control subjects, suggesting that the specificity is quite high. Such controls tend to be healthy and young. The test is more often ordered on older subjects with concomitant diseases, including those associated with false-positive results (see below). Thus, the true specificity falls well below 95%.

PROBLEMS WITH THE RF

False-Positive Test Results

The clinical utility of the RF may be undermined by rheumatic and nonrheumatic diseases that cause arthralgia or even mimic RA and are associated with a positive RF (**Tables II** and **III**). The importance of this depends on the frequency with which these diseases are encountered, the ability to diagnose them promptly by other means (e.g., positive blood cultures in endocarditis), and the ordering behavior of the clinician. Clinical contexts that are

TABLE II

Rheumatic Diseases Associated with a Positive Rheumatoid Factor

Disease	Frequency	References
Rheumatoid arthritis	50–90%	[3–5,26–28]
Systemic lupus erythematosus	15–35%	[29,30]
Sjögren's syndrome	75–95%	[31,32]
Systemic sclerosis	20–30%	[33,34]
Polymyositis/dermatomyositis	5–10%	[35]
Cryoglobulinemia	40–100%	[36–38]
Mixed connective tissue disease	50–60%	[39]

TABLE III

Nonrheumatic Conditions Associated with a Positive Rheumatoid Factor*

Condition	Frequency
Aging (> age 70)	10–25%
Infection	
Bacterial endocarditis†	25–50%
Liver disease†	15–40%
Tuberculosis	8%
Syphilis†	Up to 13%
Parasitic diseases‡	20–90%
Leprosy†	5–58%
Viral infection†§	15–65%
Pulmonary disease	
Sarcoidosis†	3–33%
Interstitial pulmonary fibrosis	10–50%
Silicosis	30–50%
Asbestosis	30%
Miscellaneous diseases	
Primary biliary cirrhosis†	45–70%
Malignancy†‖	5–25%

*References available from the author. Most reports present a small, selected, or consecutive series of patients with the nonrheumatic condition in whom RF measurements are ordered.
†Diseases that may mimic rheumatoid arthritis.
‡Chagas' disease, leishmaniasis, onchocerciasis, and schistosomiasis are the best-documented examples.
§Rubella, mumps, and influenza are the best-documented examples.
‖Leukemias and colon carcinoma are the best-documented examples.

TABLE IV

Diseases Associated with Arthritis or Arthralgia in Which Rheumatoid Factor Is Usually Absent

- Osteoarthritis
- Polymyalgia rheumatica
- Spondyloarthropathy
  - Psoriatic arthritis
  - Reiter's syndrome
  - Arthritis associated with inflammatory bowel disease
  - Ankylosing spondylitis
- Crystal-induced arthritis
  - Gout
  - Pseudogout (calcium pyrophosphate dihydrate crystal deposition disease)
  - Basic calcium phosphate (hydroxyapatite) crystal deposition disease
- Lyme disease
- *Metabolic/endocrinologic disease*
  - Acromegaly
  - Diabetes mellitus
  - Hemochromatosis
  - Hyperparathyroidism
  - Ochronosis
  - Thyroid disorders (hyperthyroidism, hypothyroidism, and thyroiditis)
  - Wilson's disease
- Amyloidosis
- Parvovirus infection
- Soft tissue disease
  - Tendinitis
  - Bursitis

associated with a positive RF but do not mimic RA (such as tuberculosis) do not impact significantly on the usefulness of RF, because, in the absence of features suggesting RA, the RF would likely not be ordered. Still other diseases may mimic RA but are usually associated with a negative RF; in these situations, the clinician must differentiate seronegative rheumatic disease, such as a spondyloarthropathy or polymyalgia rheumatica (PMR), from seronegative RA or nonrheumatic disease (see Table III and **Table IV**). Such distinctions may be quite difficult and are an important source of ambiguity for the clinician, especially considering the frequency with which these disorders are encountered in a primary care setting.

The effect of aging on the RF result should not be underestimated. While usually in low titer, the incidence of RF positivity increases from less than 5% among patients under age 55, to as high as 25% over age 70, without regard to joint disease [8–10,40,41]. Reliance on the titer of the RF to segregate true- and false-positive test results is unwise, since up to 20% of false-positive RF results in the elderly are in a titer of 1:160 or higher [40,41]. In the elderly patient with suspected rheumatic disease, the finding of a positive RF must be interpreted in the context of its lowered specificity in this population.

False-Negative Test Results

A negative RF contributes little to the diagnosis of RA in a patient who otherwise meets criteria for the disease. It may, indeed, lead the clinician away from the proper diagnosis. Therefore, despite the recognition of seronegative RA, a negative RF in RA may be considered a false-negative test result. The proportion of patients with RA who are seronegative varies among reported series, but most often represents 20% to 35% of the total. Age and gender affect the frequency of seronegative disease, as patients with elderly-onset RA and female patients are more often seronegative than nongeriatric or male patients [26,42,43]. Few studies have reported the incidence of seronegative RA in community

practice [8]. If seronegative RA does indeed occur in as much as a third or more of all patients with RA, this high false-negative rate also reduces the clinical utility of the test.

RF AS A SCREENING TEST

RF as a screening test for RA has been studied in a limited way in select populations [44,45]. Although some asymptomatic individuals destined to develop RA may apparently be detected by ordering the test, there is no preventive or early therapy known to change the course of the illness. Even if such therapy existed, many more false-positive than true-positive tests would result from such screening, as discussed above (and see Table I). This notion is further supported by population-based studies examining the prevalence of RA in which false-positive RF results were noted three to four times as often as true-positive results [23,46]. When the positive predictive values of RF could be derived from these surveys, they varied from 20% to 30%; negative predictive values ranged from 93% to 95%.

RF IN SUSPECTED RA

The RF is helpful in the evaluation of a patient with suspected RA primarily when the pretest likelihood is neither very low nor very high (Table I). Seronegative RA and false-positive test results (Table III) limit the utility of RF and obligate the clinician to rely on other clinical features to make the diagnosis. The criteria established for the classification of RA in 1958, and more recently in 1987, rely heavily on objective, clinical evidence of a symmetric polyarthritis [6,7]. RF has been retained in the most recent revision of the criteria but is only one of seven possible criteria, of which patients must satisfy four. These criteria were designed to guide classification of patients, especially as inclusion criteria for studies of RA. In clinical practice (rather than in research studies), there may well be less reliance on these criteria and even higher rates of seronegative RA. This is also suggested by population-based studies in which seropositive RA comprised the minority of RA patients [8,23,46]. By reducing the test's sensitivity, this would dilute even further the usefulness of RF in patients suspected of having RA. The possibility that a patient with seronegative RA actually has another seronegative entity (Tables III and IV) must always be considered; such patients may "falsely" reduce the apparent sensitivity of the RF.

Given the potential bias of published studies of RA to include the most unequivocal (and perhaps, therefore, the more severe) cases of RA, the true sensitivity of the RF in RA may be overestimated in medical textbooks and the rheumatologic literature. In addition, in studies of the disease, the proportion of RA patients who are seropositive varies widely [3,26,28]. Therefore, the true incidence of seropositive RA (equivalent to the sensitivity of RF as a diagnostic test) is unclear. As discussed above, the more female or elderly patients with RA included in a study or cared for in practice, the lower the incidence of seropositivity and therefore the lower the sensitivity [26,43].

RF IN ESTABLISHED RA

The usefulness of the RF among patients already known to have RA is primarily prognostic. Statistically, patients with higher-titer RF will have more severe disease [47,48], and patients who are seropositive in any titer are more likely to have severe disease than those who are RF-negative [43,47,49]. Other features correlating with RF in patients with RA include subcutaneous nodules, vasculitis, and a poorer long-term prognosis [3,50–52]. However, in an individual patient, severity of disease, including joint and extra-articular manifestations of RA, cannot be accurately predicted on the basis of RF.

Some physicians advocate use of the RF to guide therapy [53] and recommend remittive agents early in the disease when RF is present or in high titer. This is, however, not a generally accepted notion. Indeed, there is little evidence to suggest that an individual patient with RA with a highly positive RF will fare better if treated earlier or more aggressively. In addition, although the titer of RF may decrease with various therapies [54,55], this is not a generally accepted measure of improvement. Thus, the absence, presence, or level of RF in a patient with well-established RA is unlikely to add useful information.

UTILITY OF RF IN DISEASES OTHER THAN RA

In diseases other than RA, few studies address the utility of RF. Although RF is positive in a significant subset of patients with other rheumatic and nonrheumatic diseases (Tables II and III), its presence or absence probably weighs little in the diagnosis of such diseases. For instance, a positive RF in primary Sjögren's syndrome or subacute bacterial endocarditis would neither help make the appropriate diagnosis nor argue against it. Certainly, such test results could lead the clinician against the proper diagnosis (for instance, by attributing the arthralgia of endocarditis to RA or another rheumatic illness). RF is often recommended in the evaluation of fever of unknown origin (FUO) [56,57], but since prolonged, significant fever is distinctly

uncommon in RA (except for Still's disease, when RF is usually negative [58], or rheumatoid vasculitis, in which disease is usually flagrant and long-standing [50,59]), such recommendations are not well founded. In fact, in a recent series, the RF was not helpful in any patients with FUO, despite being ordered in almost every case [60]. It has, however, been suggested that the disappearance of the RF in a patient with Sjögren's syndrome may herald the onset of lymphoma [61]. Serial measurement of RF in such patients therefore may be helpful in the early detection of this complication. The RF in cryoglobulinemia is frequently positive [36–38], but actual measurement of cryoglobulins in the serum is required to make the proper diagnosis. Similarly, in rheumatic and nonrheumatic diseases associated with a positive RF (Tables II and III), clinical criteria and/or other diagnostic studies are far better indicators of the proper diagnosis than is the RF.

REQUESTS FOR RF

The RF is ordered frequently. A survey of two large commercial laboratories in the Boston area revealed that together they receive over 22,000 requests for RF each year. One Boston health maintenance organization with 275,000 members performs approximately 4,000 outpatient RF tests each year (equivalent to a RF ordered for 1.5% of members yearly). In our institution, a 500-bed teaching hospital for adult patients, approximately 1,200 requests per year are received and patients are billed $29.00 for each test. The amount of useful information derived from such large numbers of tests has not been analyzed in an adult population. One study [62] of a pediatric population found that fewer than 5% of 437 tests ordered were positive, with an observed sensitivity of 4.8%, specificity of 98%, and positive predictive value of 45%. The authors estimated that in most pediatric outpatient settings, the RF's positive predictive value would be less than 1%.

Among the 563 requests for RF received in our institution over the first 6 months of 1990, 86 (15.3%) were positive. By chart review at least 2 months after RF determination, only 21 (3.7% of total tests ordered) were in patients considered to have RA; an additional eight patients (1.4%) had another systemic rheumatic disease (two with PMR, and one each with systemic lupus erythematosus [SLE], cryoglobulinemia, Sjögren's syndrome, drug-induced lupus, reactive arthritis, and spondylitis). Thus, for the diagnosis of RA, the RF had a positive predictive value of only 24% at a cost of $777 per true-positive result; for any rheumatologic disease, its positive predictive value was 34% at a cost of $563 per true-positive result. It should be noted that a positive RF in some of these other rheumatic diseases (e.g., SLE) might argue against the proper diagnosis. Although some of the patients with a negative RF may have had seronegative RA, the RF was clearly not helpful in securing that diagnosis. The low predictive value suggests that these tests may be ordered in clinical situations associated with a low pretest likelihood of RA (or other seropositive rheumatic disease). For the 57 of 86 (66%) patients in whom the RF was positive but no rheumatic illness was detected, the information acquired was probably unhelpful and possibly misleading.

RF tests are often ordered with other tests ("the rheumatic panel") such as antinuclear antibody (ANA) or uric acid. In our institution, where tests must be ordered separately, approximately 81% of requests for RF were accompanied by requests for ANA. This strategy of ordering tests in combinations is likely to increase even more the frequency of false-positive test results [63].

CONCLUSIONS

Despite the RF's stature as a time-honored and clinically useful test, available information suggests that its usefulness is surprisingly limited. In patients considered to have RA, the test will primarily provide prognostic (albeit, limited) information. In patients with arthralgia in a distribution atypical for RA, and in patients with a systemic inflammatory disease that does not resemble RA (including FUO), the RF is likely to have very limited utility and may even be misleading. Finally, RF performs poorly as a screening test and should not be ordered in patients with minimal or no symptoms. The most useful information will be obtained when the RF is ordered in patients with a moderate pretest probability of RA, as a serial measurement in Sjögren's syndrome, and in suspected cryoglobulinemia. Recognition of the RF's limitations and more selective test ordering would reduce the expense of test performance as well as the amount of useless and misleading information obtained.

ADDENDUM

Since the preparation of this manuscript, Wolfe and colleagues [64] published an analysis of RF testing in 8,287 patients referred to an outpatient rheumatology practice. In this population, the sensitivity and specificity of the RF were 82% and 97%, respectively, while the positive and negative predictive values were 80% and 96%, respectively. The high clinical utility of the RF in their study demonstrates that in a selected population with a high

prevalence of rheumatic disease (16% in their practice), the test may perform very well. The finding of high specificity for the RF even among the aged varies with previous analyses [40,41] and requires validation by other investigators.

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