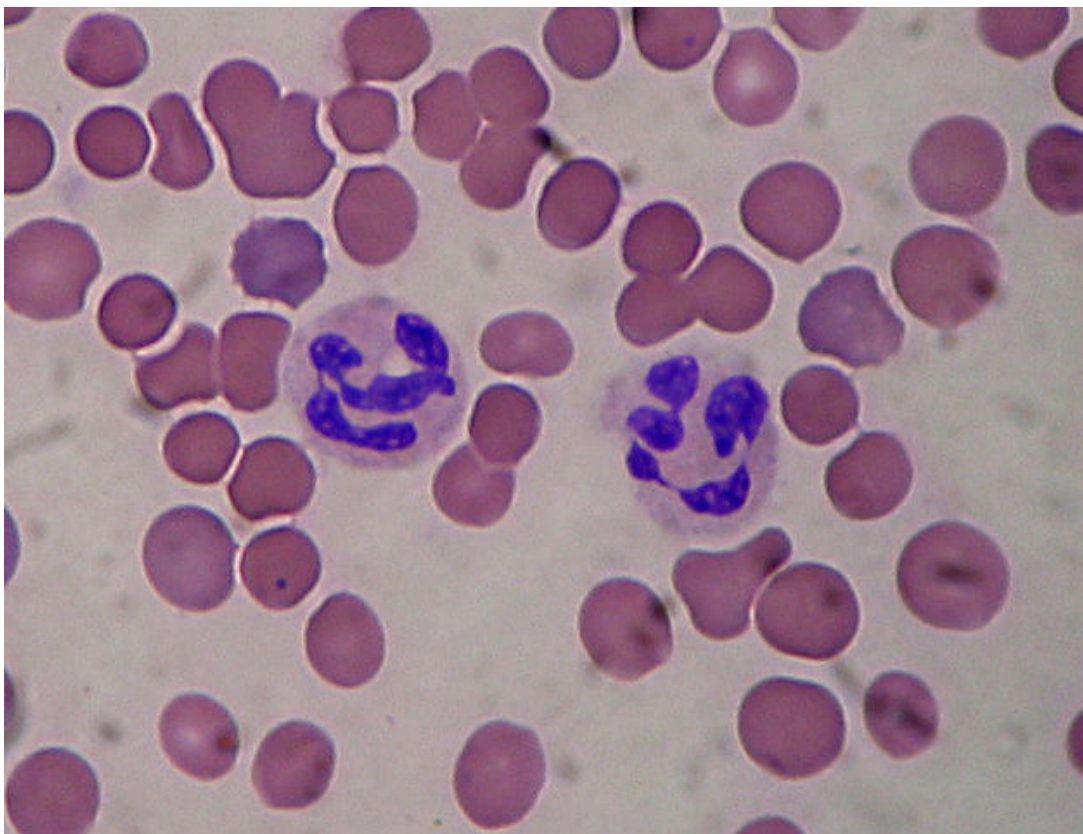


# Laboratory Evaluation in Rheumatic Diseases: Acute-phase Protein and Autoantibodies

[See online here](#)

**Rheumatic diseases are related to or caused by an abnormal immune response that commonly involves autoantibodies. The detection of these autoantibodies in the laboratory evaluation of a patient suspected to have a rheumatic disease can help in confirming the diagnosis and monitor the prognosis or response to treatment in rheumatic diseases.**



## Overview

There more than 100 rheumatic diseases that are characterized by inflammation against supportive and connective tissues of the body such as joints, bones, and muscles. They arise from the body mounting an immune response against harmless antigens that are located in the body due to cross-reactivity of these antigens with harmful antigens.

Autoantibodies, when detected, **can confirm the preliminary diagnosis** of autoimmune diseases, and identify disease activity. Unfortunately, the detection of these autoantibodies in a healthy individual is common, and their absence in a patient with a

suspected rheumatic disease does not exclude the diagnosis.

Thus, there is no specific diagnostic test for most of the rheumatic diseases and correlation of various findings is applied.

## Acute Phase Proteins

Rheumatic diseases are characterized by chronic [inflammation](#).

**Inflammation is associated with an increase in the levels of:**

- Ceruloplasmin
- Erythrocyte sedimentation rate
- C-reactive protein
- Ferritin
- Haptoglobin
- Fibrinogen
- Alpha-1 antitrypsin and amyloid A.

Ceruloplasmin, C-reactive protein, ferritin, haptoglobin, fibrinogen, and amyloid A are known as acute-phase proteins, and an elevation in any of them is indicative of inflammation. Acute phase reactants might be also elevated in infections and malignancy. The most commonly used acute-phase proteins/reactants are the erythrocyte sedimentation rate and the C-reactive protein.

An elevated erythrocyte sedimentation rate equals and elevation of fibrinogen because red blood cell aggregation is mainly affected by fibrinogen. Therefore, the erythrocyte sedimentation rate can be considered as an indirect assessment of the acute phase protein, fibrinogen.

## ESR

ESR represents the rate at which red blood cells settle. It is directly proportional to age and thus normal levels vary as follows :

**The normal erythrocyte sedimentation rate (ESR) can be estimated using the following formulas in males and females:**

- ESR in males = age / 2
- ESR in females = (age + 10) / 2

The C-reactive protein is another acute-phase protein that is elevated in case of inflammation. The serum levels of C-reactive protein might be elevated up to 1000 times when the patient develops an inflammatory condition. The C-reactive protein is synthesized in the liver. The C-reactive protein levels are not dependent on the age or sex of the patient making them a more robust assessment of inflammatory conditions.

False positives are seen with malignancy, anemia and infective processes. The test is used to monitor patients with fibromyalgia and polymyalgia rheumatica.

## C-reactive protein (CRP)

**The normal C-reactive protein (CRP) levels can be summarized in the following:**

- Normal < 0.2 mg/dL
- Indeterminate 0.2 to 1.0 mg/dL

- Inflammation > 1.0 mg/dL
- Infectious etiology > 10 mg/dL

## Acute Phase Reactants in Rheumatic Diseases

### Rheumatoid Arthritis



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In patients with rheumatoid arthritis, the **CRP levels are elevated**. This is useful in distinguishing patients with [rheumatoid arthritis](#) from those with osteoarthritis. A highly elevated CRP level early in the disease is indicative of severe progressive erosive rheumatoid arthritis. CRP levels can be used to monitor disease activity in rheumatoid arthritis. ESR levels are also elevated in rheumatoid arthritis, however, the sensitivity of ESR in rheumatoid arthritis is low compared to CRP.

### Ankylosing spondylitis and Psoriatic Arthritis

CRP levels are elevated only in half of the patients with ankylosing spondylitis. Patients with ankylosing spondylitis and peripheral arthritis or uveitis have markedly elevated CRP levels. ESR levels are also elevated in half of the cases, however, the ESR levels in this group of patients are not correlated with disease severity.

### Systemic Lupus Erythematosus

ESR levels are usually elevated in systemic lupus erythematosus, however, CRP levels are frequently normal. In fact, asymptomatic elevation in ESR might be the first manifestation of systemic lupus erythematosus in some patients. An elevated CRP in a patient with systemic lupus erythematosus is suggestive of early atherosclerosis.

## Autoantibodies

### Rheumatoid Factor

The rheumatoid factor (RF) is a **specific antibody against the Fc section of immunoglobulins**. The most common structure of RF is the IgM structure.

A positive RF does not mean that one has rheumatoid arthritis. However, up to 70% of

rheumatoid arthritis patients, have a positive RF test. The role of RF in the pathogenesis of rheumatoid arthritis is still poorly understood, however, it is likely to be related to impaired antigen presentation and amplified humoral response.

A positive RF might be indicative of worse prognosis in patients with rheumatoid arthritis.

**Positive and elevated RF levels are associated with:**

- Aggressive joint disease
- Rheumatoid nodules
- Extra-articular involvement.

In up to 15% of healthy individuals, the RF level is positive. Therefore, the sole presence of RF is not sufficient to make the diagnosis of rheumatoid arthritis. RF levels are also elevated in patients with systemic lupus erythematosus, cryoglobulinemia, pulmonary interstitial fibrosis and silicosis, and in Sjogren’s syndrome. Up to one-third of the patients with rheumatoid arthritis are seronegative (do not have RF).

One should ask for RF only after the proper clinical evaluation of the patient and only when rheumatoid arthritis is suspected based on the clinical findings.

## Anti-citrullinated peptide antibodies

The most type of anti-citrullinated peptide antibodies (ACPAs) is the **anti-perinuclear factor**. Other common ACPAs include an anti-keratin antibody, anti-filaggrin, anti-Sa, and anti-cyclic citrullinated peptide (anti-CCP). Anti-CCP is highly specific for rheumatoid arthritis compared to other autoantibodies including RF.

Anti-CCP antibodies are detected years before the development of any rheumatoid arthritis symptoms. Patients with positive anti-CCP antibodies early in the disease are more likely to have erosive disease compared to those who do not. Anti-CCP titrations are not used in clinical practice because anti-CCP levels are not correlated with disease activity and are useless in monitoring the disease.

## Antibodies Against Nuclear Antigens

**Anti-nuclear antibodies** (ANA) include antibodies that act against the DNA, RNA, histones, centromeres, nucleolus, and other nucleoproteins. The most commonly used ANAs in clinical practice are those against DNA or RNA.

ANAs include two types of antibodies: antibodies against DNA and histones, and antibodies against extractable nuclear antigens. Antibodies against DNA and histones are elevated in systemic lupus erythematosus and drug-induced lupus erythematosus.

ANA tests are quite specific and sensitive for systemic lupus erythematosus and scleroderma. In patients with drug induce systemic lupus erythematosus and mixed connective tissue disease, a positive ANA is diagnostic.

**The other specific ANAs in rheumatic diseases can be summarized in the following:**

<b>Anti-dsDNA</b>	Diagnostic of SLE with a specificity of 97.4% and sensitivity of 57.3%
<b>Anti-Sm</b>	Diagnostic of SLE with a specificity of almost 100% but low sensitivity of 25%

<b>Anti-RNP</b>	Their presence is diagnostic of mixed connective tissue disease
<b>Anti-histone antibodies</b>	They are present in up to 95% of those with drug-induced lupus erythematosus
<b>Anti-chromatin</b>	They are present in 50 to 90% of systemic lupus erythematosus patients
<b>Anti-Ro/SSA and anti-La/SSB</b>	They are found in systemic scleroderma and are diagnostic of the condition. They are also detected in patients with systemic lupus erythematosus
<b>Anti-centromere</b>	Antibodies against the centromere protein B (CENP-B) are found in patients with limited cutaneous systemic sclerosis and in patients with CREST syndrome
<b>Anti-neutrophil cytoplasmic antibodies (ANCA)</b>	Detected in patients with Wegener's granulomatosis, pauci-immune glomerulonephritis, microscopic polyangiitis, and Churg-Strauss syndrome
<b>Anti-Mi2 antibodies</b>	Detected in patients with dermatomyositis. Anti-SRP antibodies are detected in autoimmune heart disease and myositis. Anti-MAS antibodies are found in rhabdomyolysis

## References

Birtane M, Yavuz S, Taştekin N. Laboratory evaluation in rheumatic diseases. World Journal of Methodology. 2017;7(1):1-8. doi:10.5662/wjm.v7.i1.1.

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