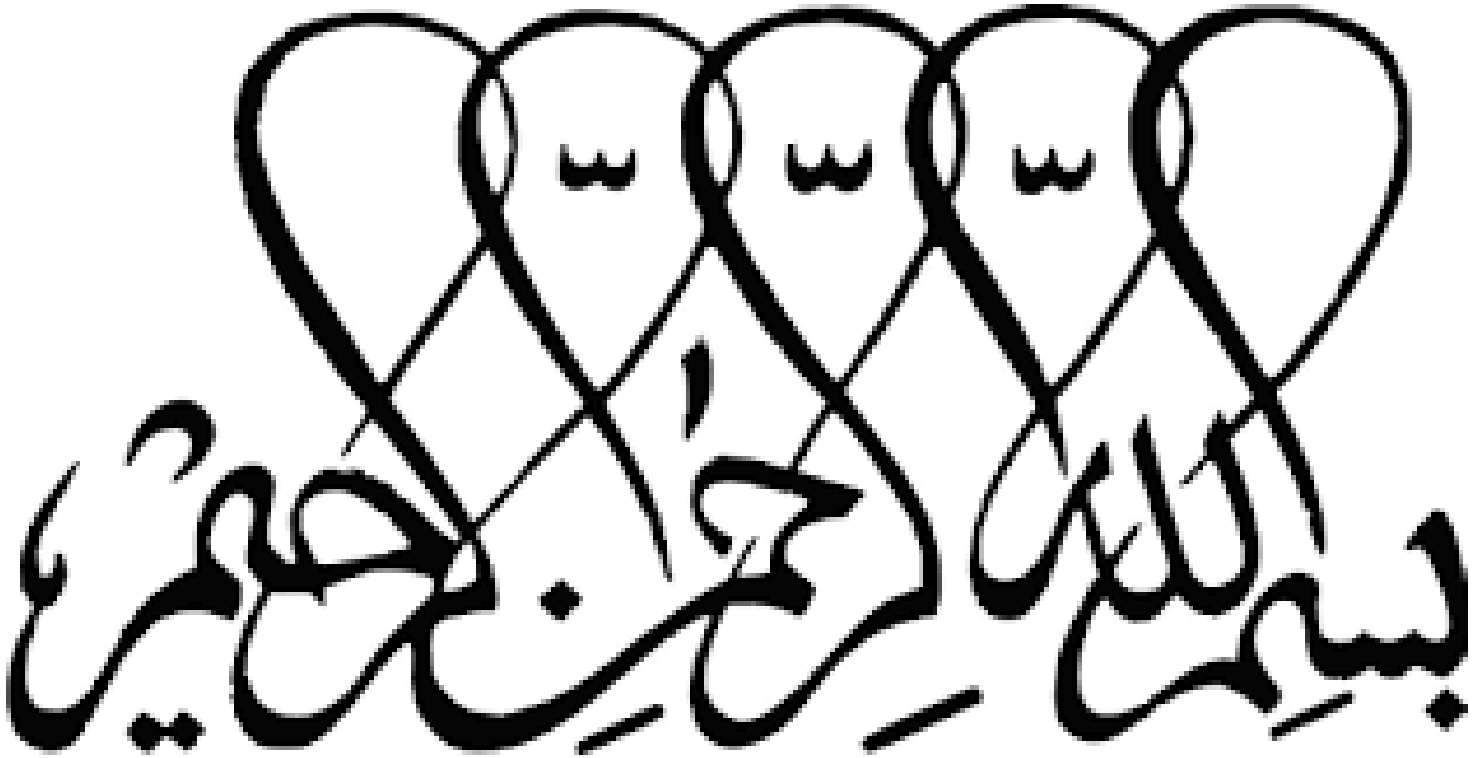
بسم الله الرحمن الرحيم


Tabriz University of
Medical Sciences

Diagnostic Tests & Procedures in Rheumatic Diseases

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Tabriz Medical science University
Jun 2023
1402/3/31

Paraclinic in Rheumatic Diseases

_Lab Tests •

Non Specific •

Spesific tests •

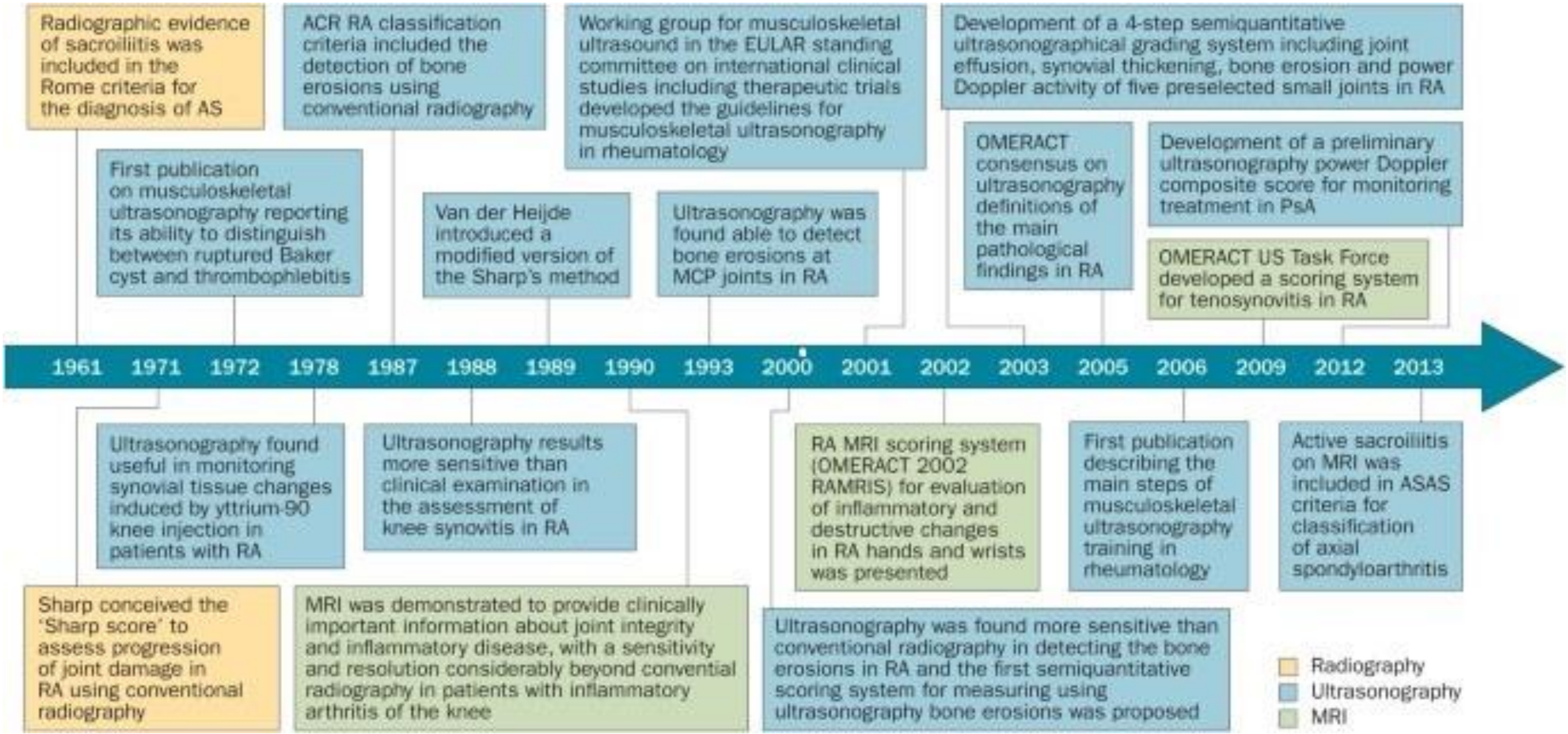
_Imagings •

_EMG- NCV •

_Biopsy •

What is the difference between CRP and hs-CRP?

The hs-CRP test is different than the standard CRP test. The standard test measures high levels of the protein to find different diseases that cause inflammation. The hs-CRP test measures low levels and focuses on the risk of heart disease and stroke.


Radiographic evidence of sacroiliitis was included in the Rome criteria for the diagnosis of AS
ACR RA classification criteria included the detection of bone erosions using conventional radiography
Working group for musculoskeletal ultrasound in the EULAR standing committee on international clinical studies including therapeutic trials developed the guidelines for musculoskeletal ultrasonography in rheumatology
Development of a 4-step semiquantitative ultrasonographical grading system including joint effusion, synovial thickening, bone erosion and power Doppler activity of five preselected small joints in RA
First publication on musculoskeletal ultrasonography reporting its ability to distinguish between ruptured Baker cyst and thrombophlebitis
Van der Heijde introduced a modified version of the Sharp's method
Ultrasonography was found able to detect bone erosions at MCP joints in RA
OMERACT consensus on ultrasonography definitions of the main pathological findings in RA
Development of a preliminary ultrasonography power Doppler composite score for monitoring treatment in PsA
OMERACT US Task Force developed a scoring system for tenosynovitis in RA
1961
1971
1972
1978
1987
1988
1989
1990
1993
2000
2001
2002
2003
2005
2006
2009
2012
2013
Ultrasonography found useful in monitoring synovial tissue changes induced by yttrium-90 knee injection in patients with RA
Ultrasonography results more sensitive than clinical examination in the assessment of knee synovitis in RA
RA MRI scoring system (OMERACT 2002 RAMRIS) for evaluation of inflammatory and destructive changes in RA hands and wrists was presented
First publication describing the main steps of musculoskeletal ultrasonography training in rheumatology
Active sacroiliitis on MRI was included in ASAS criteria for classification of axial spondyloarthritis
Sharp conceived the 'Sharp score' to assess progression of joint damage in RA using conventional radiography
MRI was demonstrated to provide clinically important information about joint integrity and inflammatory disease, with a sensitivity and resolution considerably beyond convential radiography in patients with inflammatory arthritis of the knee
Ultrasonography was found more sensitive than conventional radiography in detecting the bone erosions in RA and the first semiquantitative scoring system for measuring using ultrasonography bone erosions was proposed
Radiography
Ultrasonography
MRI

Diagnostic value of anti-MCV antibodies in differentiating early inflammatory arthritis

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Methods In 917 patients with recent-onset arthritis (566 RA, 351 other diseases) and in 99 healthy controls the anti-MCV, anti-CCP2 and anti- CCP3.1 tests were performed and the test characteristics compared.

Results Comparison of the tests for differentiating RA from other causes of arthritis showed a lower specificity for anti-MCV (82.9%) than for anti-CCP2 (93.4%) and anti-CCP3.1 (90.0%). Similarly, the positive likelihood ratio for anti-MCV was also lower (3.6, compared with 8.7, 5.8 for anti-CCP2 and anti-CCP3.1). The anti-MCV test had a higher sensitivity (62% vs 56.9% and 58.1%, respectively). In psoriatic arthritis, spondyloarthropathy and other arthritis anti-MCV antibodies had a prevalence of 15.2%, 13.9% and 19.4%.

Conclusion **The diagnostic performance of the anti-MCV test in the differential diagnosis of early arthritis is lower than that of the anti-CCP tests.**

Biopsy in Rheumatic Diseases

In rheumatic diseases such as acute rheumatic fever, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, dermatomyositis and tuberculous arthritis, biopsy often helps to pinpoint a diagnosis. Many tissue changes, however, are nonspecific and the pathologist must interpret them in light of clinical information.

Does CRP show all inflammation?

The majority of healthy adults have levels less than 0.3 mg/dL. However, **a low CRP level does not always mean that there is no inflammation present.** Levels of CRP may not be increased in people with **rheumatoid arthritis and lupus**.

Positive acute phase proteins	
Complement system	C3 C4 C9 C4b-binding protein
Coagulation and fibrinolytic system	Fibrinogen Plasminogen Tissue plasminogen activator Protein S Plasminogen-activator inhibitor 1
Anti-proteases α1-Protease inhibitors	Anti-chymotrypsin Pancreatic secretory trypsin inhibitor
Transport proteins	Ceruloplasmin Haptoglobin Hemopexin
Participants in inflammatory responses	Phospholipase A Lipopolysaccharide-binding protein Granulocyte colony-stimulating factor
Others	C-reactive protein Serum amyloid A α1-acid glycoprotein
Negative acute phase proteins	
Albumin Transferrin Alpha-fetoprotein Thyroxin-binding globulin Insulin-like growth factor I Factor XII	

	Lupus flare (n = 28)	Infection (n = 25)	p value
ESR (mm/hour)	50.7 (31.3)	53.4 ± (34.5)	NS
CRP (mg/dl)	5.4 (6.5)	11.2 (7.2)	0.0035
ESR:CRP ratio			0.000
≤ 2	0 (0)	3 (12.0)	
2 – 15	13 (46.4)	21 (84.0)	
≥ 15	15 (53.6)	1 (4.0)	
WBC > 10K/mm^3	6 (21.4)	5 (20)	NS

The Fever That Cries Wolf

Distinguishing the cause of fevers in patients with lupus

Highlights

- CRP is a valuable marker and regulator of systemic inflammation in RA.
- CRP levels appear to be associated with common comorbidities of RA.
- CRP appears to play a direct role in bone destruction and disease progression in RA.
- Pentameric and monomeric isoforms of CRP have different effects.
- Stratification by CRP level in clinical trials may provide valuable information.

What is the correlation between ESR and CRP?

CRP concentration peaks rapidly, approximately 48 hours after the inflammatory stimulus. When the stimulus for production stops, CRP decreases quickly. ESR is an indirect measure of inflammation. **ESR levels increase at a slow rate in response to inflammation and can take weeks to return to normal levels.**

What if ESR and CRP both are high?

Patients with high CRP but normal ESR **typically have infection, ischemia, or thromboembolism.** Patients with high ESR but normal CRP may have systemic inflammatory or autoimmune processes, including those associated with malignancy.

Can stress cause high ESR and CRP?

CRP is elevated in chronic stress and may be the link between stress and low-grade inflammation-related diseases.

Scientists found that both psychological and social stress significantly impacts CRP

How long does ESR and CRP stay elevated?

CRP may remain elevated for up to 6 weeks and ESR for up to 26 weeks after prosthetic joint surgery. Serum IL-6, CRP, and ESR have the best diagnostic value. Likelihood of infection very low if both ESR and CRP are normal. Procalcitonin has a low sensitivity.

Paraclinic in Rheumatology

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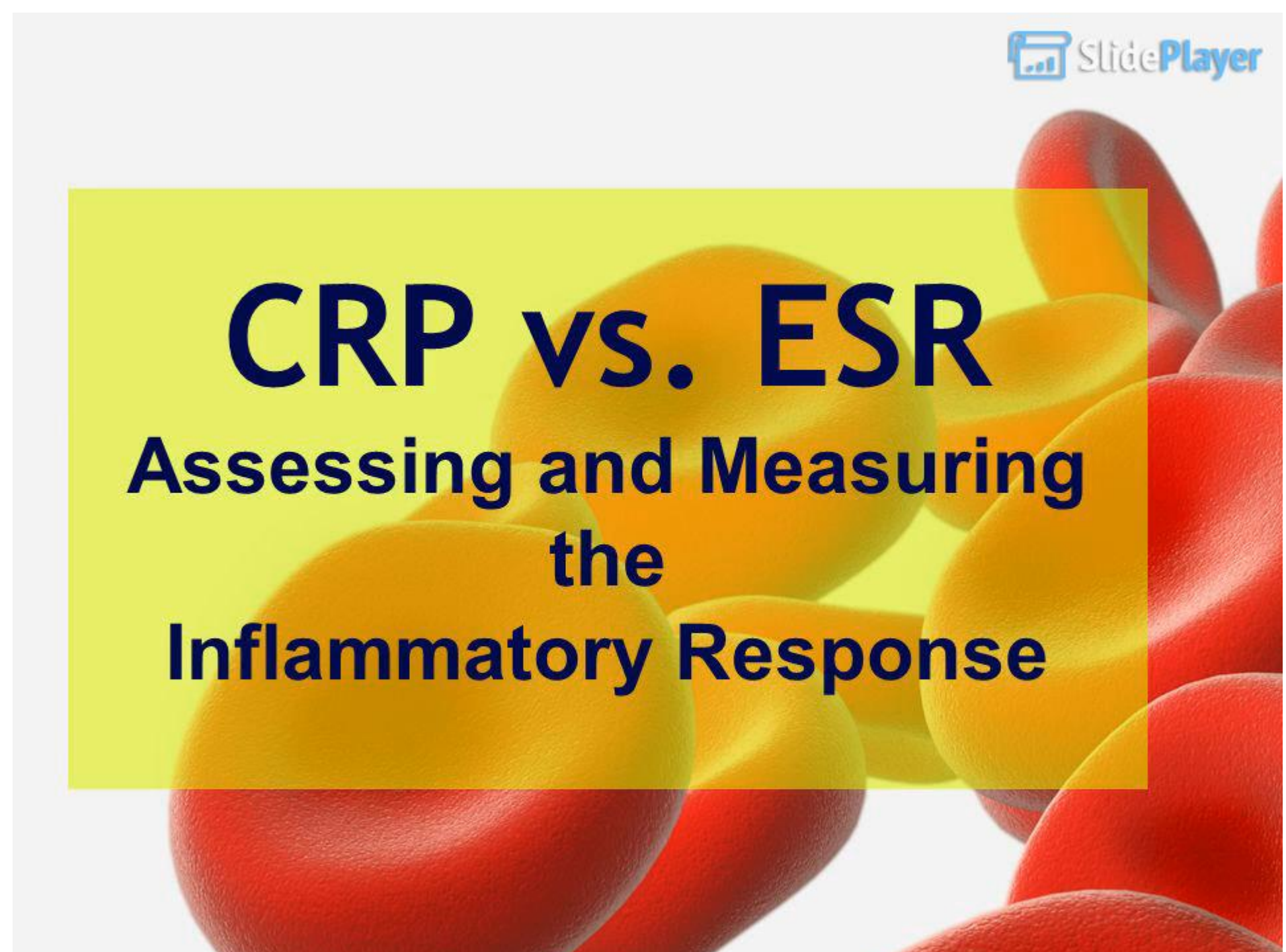


CRP vs. ESR

Assessing and Measuring the Inflammatory Response

RHEUMATOLOGY.PHYSIO ONLINE.

Rheumatology Conditions

Blood Test Profiles

	Test					
	ESR (Raised)	CRP (Raised)	Anti-CCP	HLA-B27	RF +ve	ANA +ve
RA	Often	Often	+ve	-ve	Often	Sometimes
AxSpA	Often	Often	-ve	+ve	Sometimes	Sometimes
PSpA	Often	Often	-ve	+ve	-ve	Sometimes
PsA	Often	Often	-ve	+ve	-ve	Sometimes
Lupus	Sometimes	Sometimes	-ve	-ve	Sometimes	Very Often
PMR	Very Often	Very Often	-ve	-ve	Sometimes	Sometimes
OA	Sometimes	Sometimes	-ve	-ve	Sometimes	Sometimes
Fibro	Very Rarely	Very Rarely	-ve	-ve	Sometimes	Sometimes

Is ESR and CRP always elevated in rheumatoid arthritis?

Erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) – **Both the ESR and CRP are typically elevated in RA.** These may also be repeated subsequent to the initial evaluation and diagnosis for assessment and monitoring of systemic inflammation, as indicated, over the course of disease.

When should we worry about our ESR?

ESR levels higher than 100 mm/hr could suggest a serious disease, such as infection, heart disease, or cancer .

ESR levels higher than normal may predict cancer or cancer progression, like metastasis.

What can falsely increase ESR?

Falsely elevated ESR results may be caused by fibrinogen, gamma globulins, and/or high room temperature.

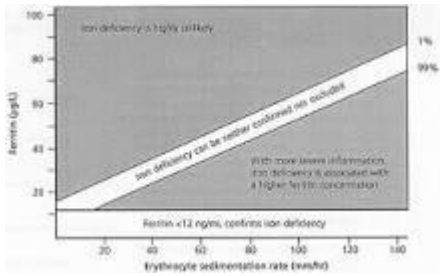
Can stress affect ESR?

Although **the mechanism for the increases in ESR in response to stressor exposure remains unclear**, it is concluded that when using the ESR in clinical practice, allowance should be made for situational factors such as the patient having experienced some stressful days and sleepless nights.

Can depression cause high ESR?

The correlation between the ESR and depression was controversial. Li et al showed that no correlation between ESR and depression in rheumatoid arthritis. While Bianciardi et al reported increase of ESR serum level in perinatal women and comorbid depression, which was in agreement with our findings.

Can anemia cause high ESR?



Anemia and macrocytosis increase the ESR. In anemia, with the hematocrit reduced, the velocity of the upward flow of plasma is altered so that red blood cell aggregates fall faster.

Significance of elevated cobalamin (vitamin B12) levels in blood

Elevated levels of serum cobalamin may be a sign of a serious, even life-threatening, disease. Hematologic disorders like chronic myelogeneous leukemia, promyelocytic leukemia, polycythemia vera and also the hypereosinophilic syndrome can result in elevated levels of cobalamin.

Not surprisingly, a rise of the cobalamin concentration in serum is one of the diagnostic criteria for the latter two diseases.

The increase in circulating cobalamin levels is predominantly caused **by enhanced production of haptocorrin.** Several liver diseases like acute hepatitis, cirrhosis, hepatocellular carcinoma and metastatic liver disease can also be accompanied by an increase in circulating cobalamin.

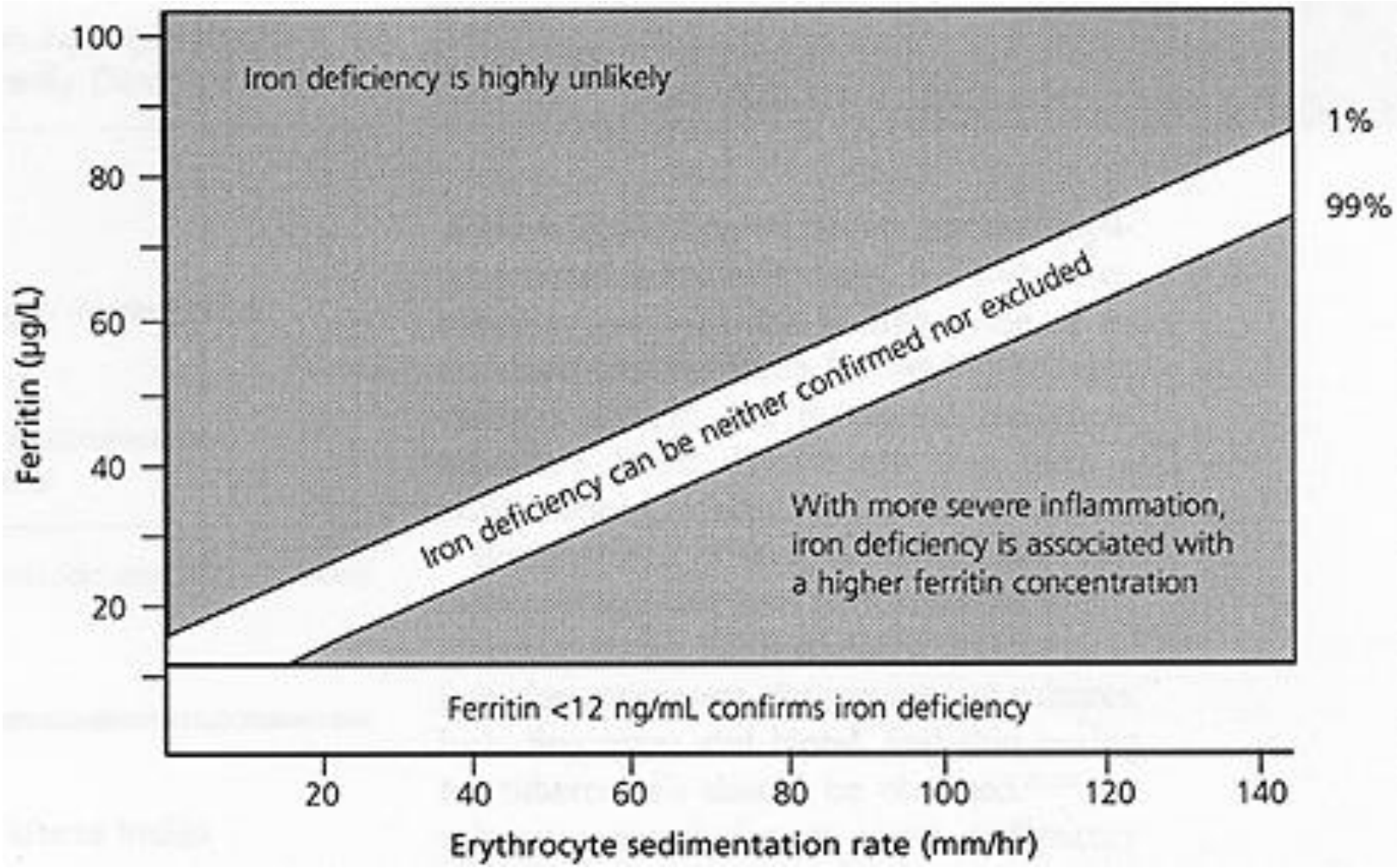
This phenomenon is predominantly caused by **cobalamin release** during hepatic cytolysis and/or **decreased cobalamin clearance** by the affected liver. Altogether it can be concluded that an observed elevation of cobalamin in blood merits the a full diagnostic work up to assess the presence of disease.

[Hypervitaminosis B12 - a new marker and predictor of prognostically unfavorable diseases]

A high serum vitamin B12 level (hypercobalaminemia) is a underestimated anomaly. Clinically, it can be paradoxically accompanied by signs of deficiency, which are related to defects in tissue uptake of vitamin B12.

The increase in the level of serum cobalamin occurs mainly in serious diseases that require early diagnosis: hemoblastosis, liver and kidney diseases, etc.

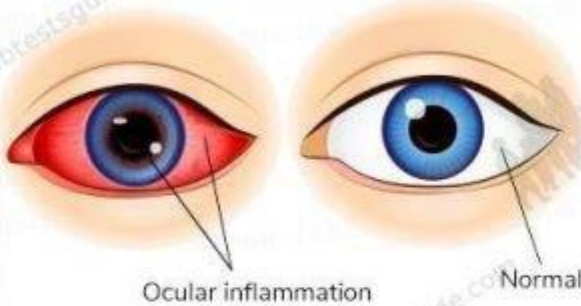
This review presents data on the metabolism of vitamin B12 and the potential significance of increasing its level as a marker for the early diagnosis of these diseases.

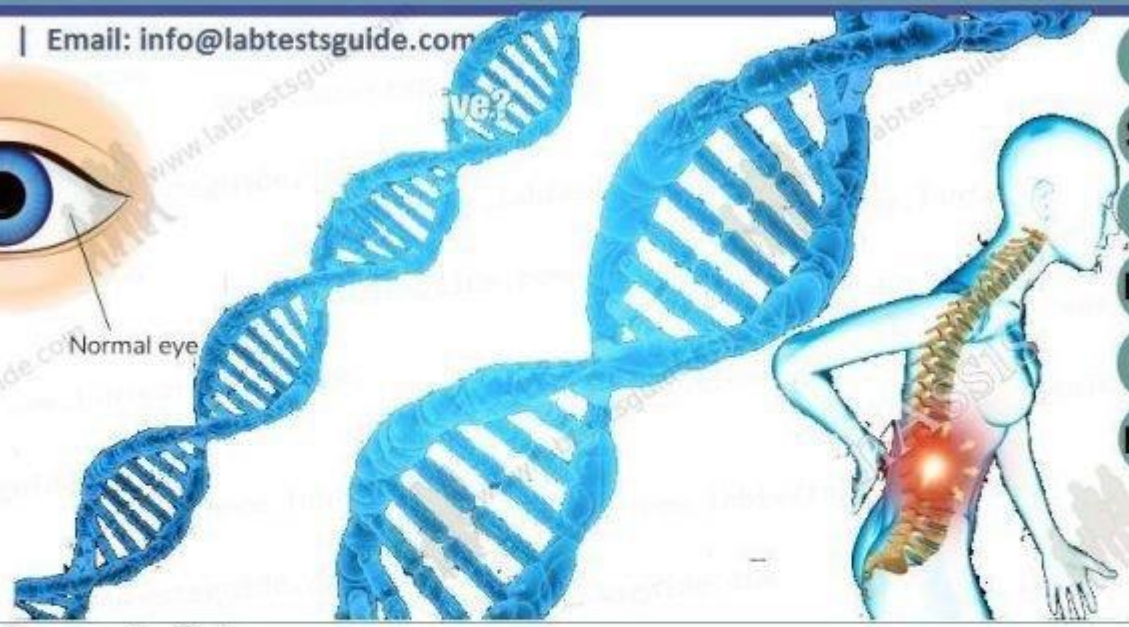

Iron deficiency is highly unlikely
Iron deficiency can be neither confirmed nor excluded
With more severe inflammation, iron deficiency is associated with a higher ferritin concentration
Ferritin <12 ng/mL confirms iron deficiency
1%
99%
Ferritin (µg/L)
100
80
60
40
20
20
40
60
80
100
120
140
Erythrocyte sedimentation rate (mm/hr)

Age and Gender	Normal ESR Value
Newborn	0-2 mm
6 months to puberty	5 to 13 mm
Men < 50 years old	15 mm
Women < 50 years old	20 mm or less
Men > 50 years old	20 mm or less
Women > 50 years old	30 mm or less

HLA-B27 Test Purpose, Procedure, Result and more

web: www.labtestsguide.com | Email: info@labtestsguide.com





Fasting	No Need
Sample	4 ml in EDTA Tube
UNIT	N/A
N.Value	Negative
Report	2-3 days
Method	Flow Cytometry

95% - Ankylosing Spondylitis
80% - Reiter's Syndrome (Reactive Arthritis)
70% - Psoriatic Arthritis (Spondylitis with Psoriasis)
50% - Enteropathic Arthritis (Spondylitis with Inflammatory Bowel Disease
6-8% - Incidence in general population without disease

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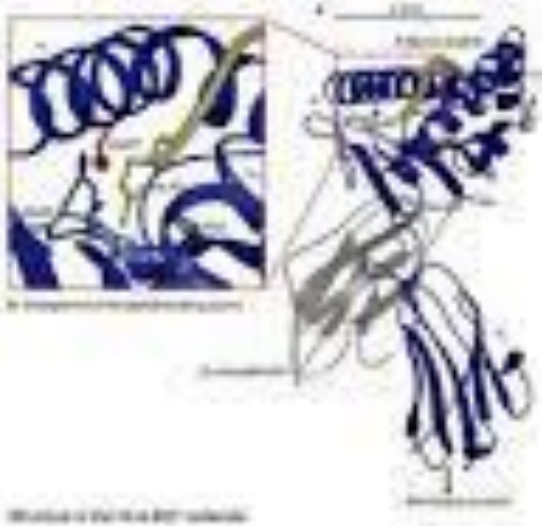
HLA B27

- **Human Leukocyte Antigen (HLA) B27** is a surface antigen encoded by the B locus in the major histocompatibility complex (MHC) on chromosome 6 and presents antigenic peptides to T cells.
- It lies on the surface of WBC.
- HLA-B27 is strongly associated with ankylosing spondylitis , and other associated inflammatory diseases referred to as "spondyloarthropathies".
- More than 100 disease associations have been made, including many ocular diseases and systemic diseases with specific ocular manifestations.

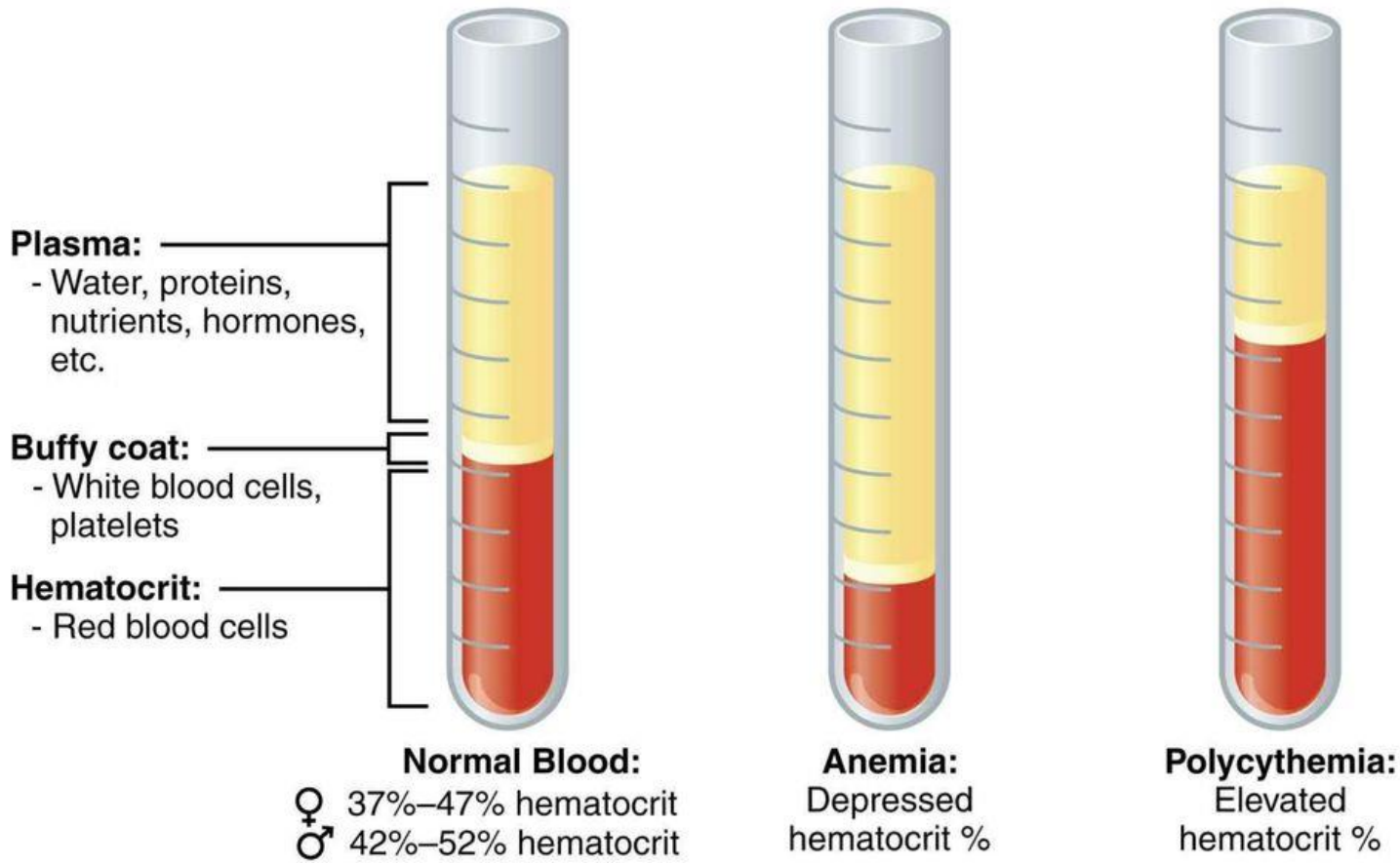


Description

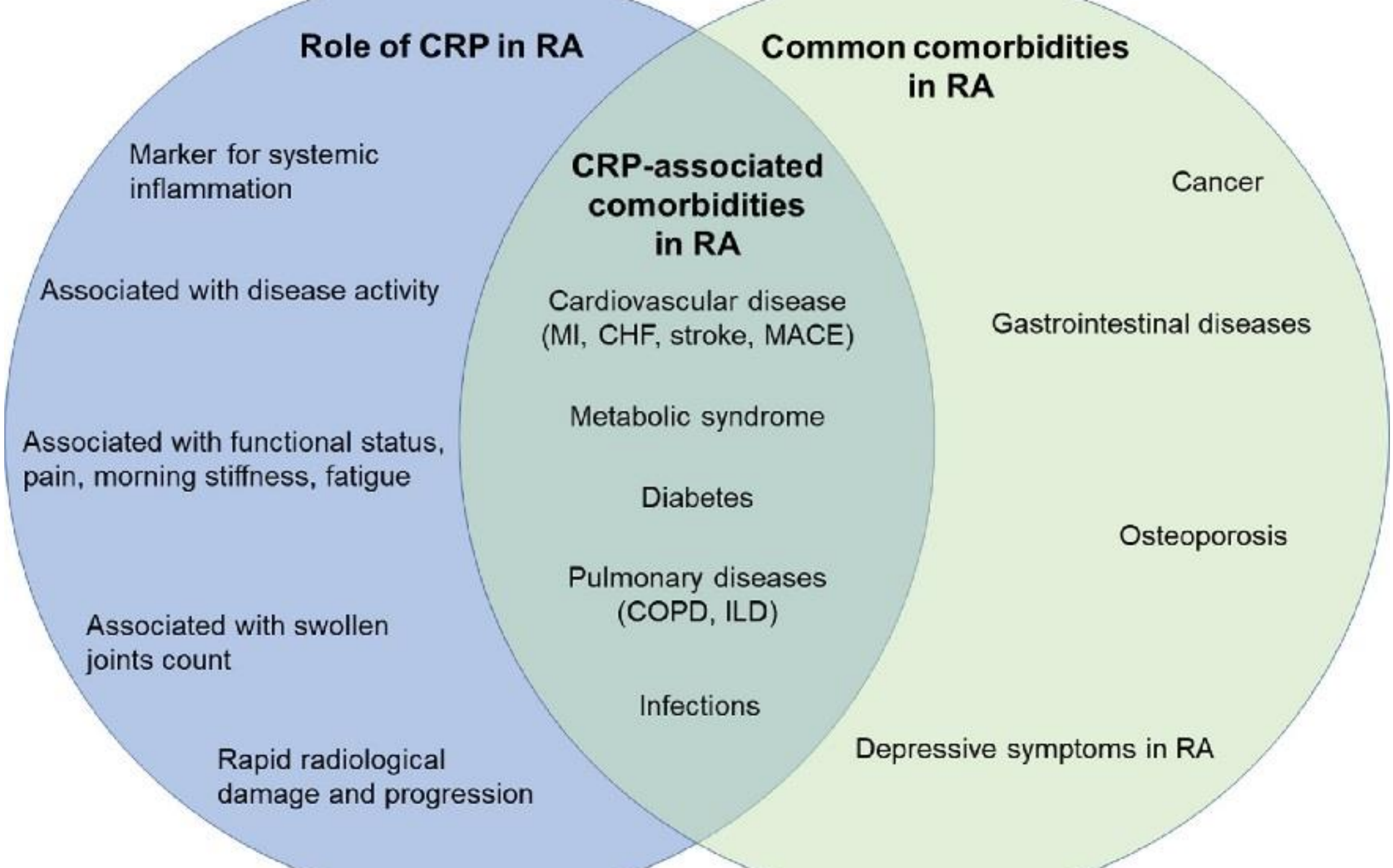
- The ESR test is a simple test.
- A specific amount of diluted, unclotted blood is placed in a special narrow tube and left undisturbed for exactly one hour.
- The red cells settle towards the bottom of the tube, and the pale yellow liquid (plasma) rises to the top.
- After 60 minutes, measurements are taken of the distance the red cells traveled to settle at the bottom of the tube.
- Most laboratories use the Westergren method.
- Normally red cells don't settle far toward the bottom of the tube. Many diseases make extra or abnormal proteins that cause the red cells to move close together, stack up, and form a column (rouleaux). In a group, red cells are heavier and fall faster. The faster they fall, the further they settle, and the higher the ESR.

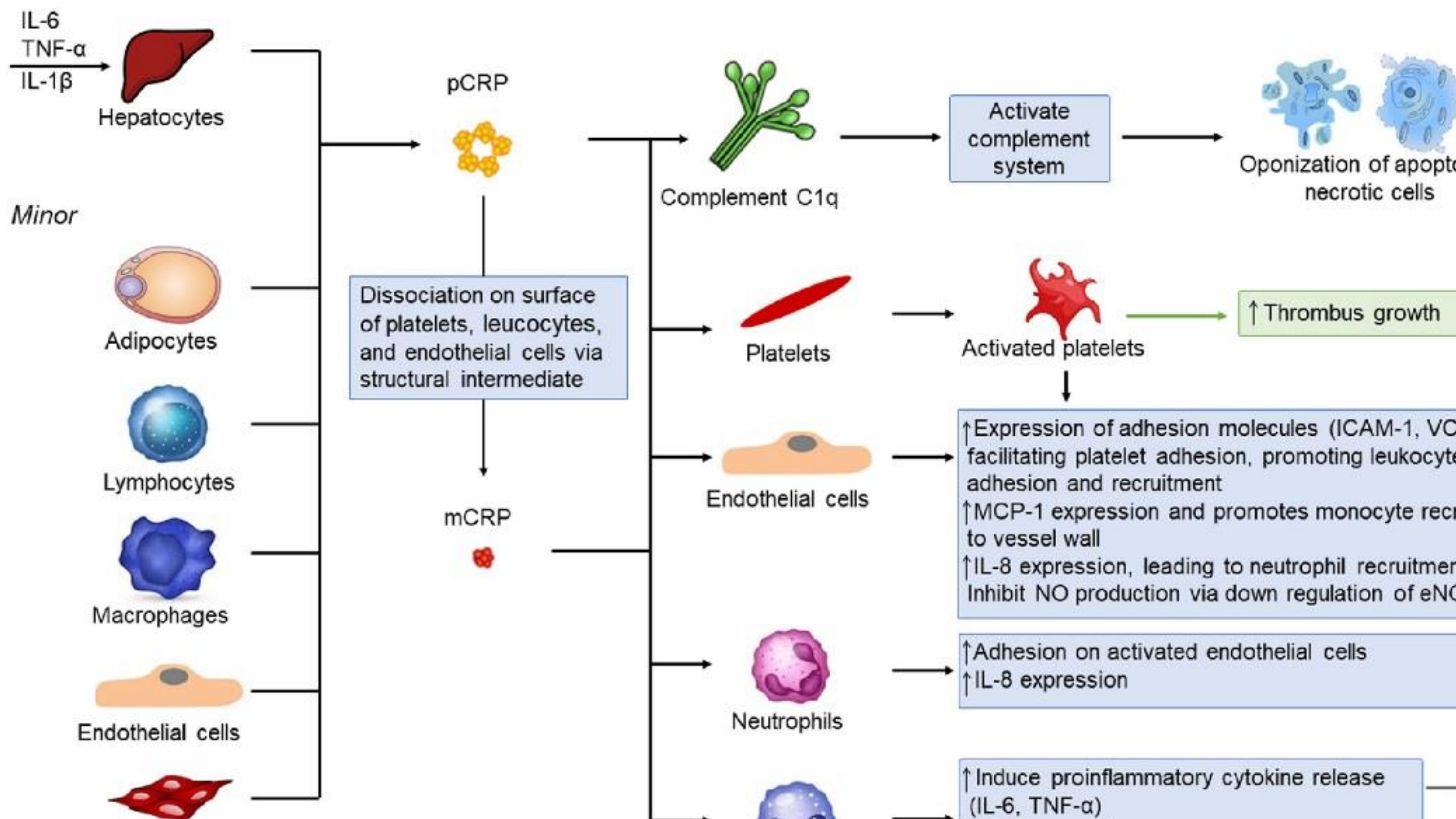
- ESR is said to be a non-specific test because an elevated result often indicates the presence of inflammation but does not tell the health practitioner exactly where the inflammation is in the body or what is causing it.
- An ESR can be affected by other conditions besides inflammation. For this reason, the ESR is typically used in conjunction with other tests, such as C-reactive protein.
- ESR is used to help diagnose certain specific inflammatory diseases, temporal arteritis, systemic vasculitis and polymyalgia rheumatica. A significantly elevated ESR is one of the main test results used to support the diagnosis
- This test may also be used to monitor disease activity and response to therapy in both of the above diseases as well as some others, such as systemic lupus erythematosus (SLE).

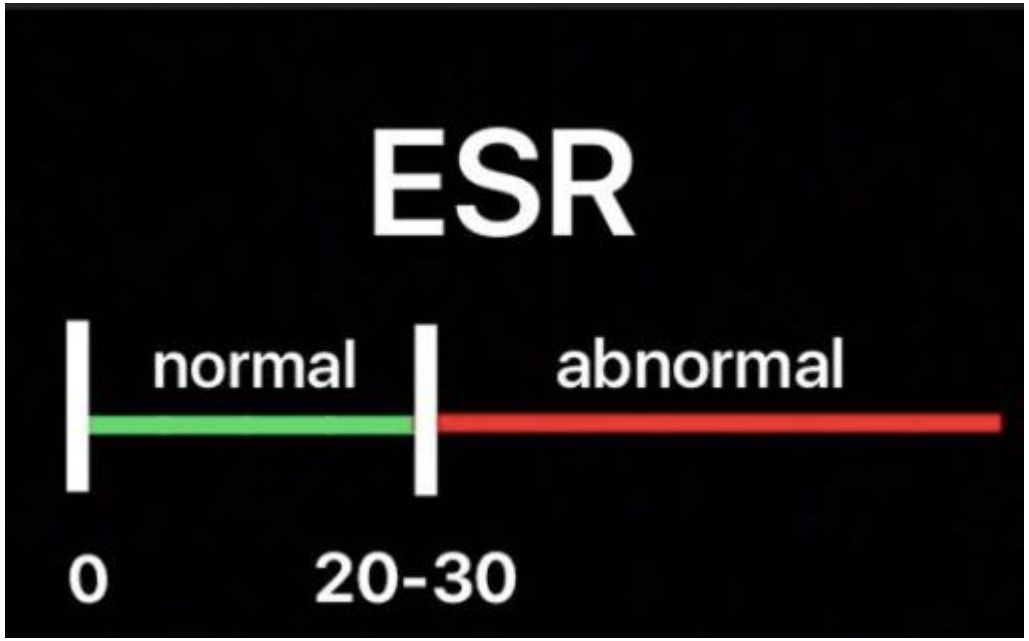
- A low ESR can be seen with conditions that inhibit the normal sedimentation of red blood cells, such as a high red blood cell count (polycythemia), significantly high white blood cell count (leukocytosis), and some protein abnormalities.
- ESR and C-reactive protein (CRP) are both markers of inflammation.

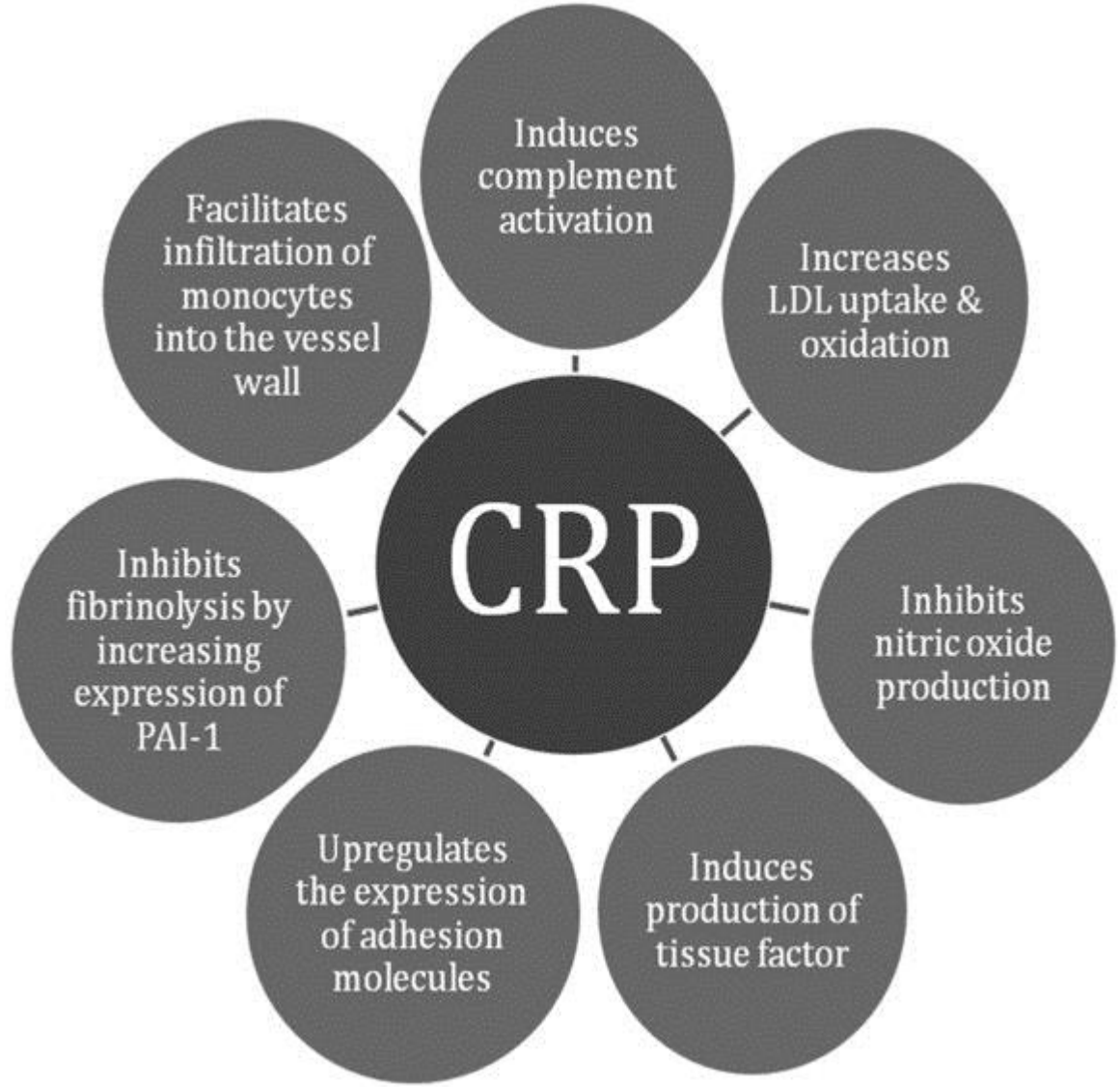

Plasma:
- Water, proteins, nutrients, hormones, etc.
Buffy coat:
- White blood cells, platelets
Hematocrit:
- Red blood cells
Normal Blood:
♀ 37%–47% hematocrit
♂ 42%–52% hematocrit
Anemia:
Depressed hematocrit %
Polycythemia:
Elevated hematocrit %

Females tend to have slightly increased erythrocyte sedimentation rates compared to males. Pregnancy and aging may also increase the ESR. Anemia, RBC abnormalities, technical factors such as tilted ESR tubes, increased temperature of the specimen, and dilution errors may increase the ESR.


Role of CRP in RA
Marker for systemic inflammation
Associated with disease activity
Associated with functional status, pain, morning stiffness, fatigue
Associated with swollen joints count
Rapid radiological damage and progression
CRP-associated comorbidities in RA
Cardiovascular disease (MI, CHF, stroke, MACE)
Metabolic syndrome
Diabetes
Pulmonary diseases (COPD, ILD)
Infections
Common comorbidities in RA
Cancer
Gastrointestinal diseases
Osteoporosis
Depressive symptoms in RA


IL-6
TNF-α
IL-1β
Hepatocytes
pCRP
Complement C1q
Activate complement system
Oponization of apopto
necrotic cells
Minor
Adipocytes
Lymphocytes
Macrophages
Endothelial cells
Dissociation on surface of platelets, leucocytes, and endothelial cells via structural intermediate
mCRP
Platelets
Activated platelets
↑Thrombus growth
Endothelial cells
↑Expression of adhesion molecules (ICAM-1, VC
facilitating platelet adhesion, promoting leukocyte
adhesion and recruitment
↑MCP-1 expression and promotes monocyte recr
to vessel wall
↑IL-8 expression, leading to neutrophil recruitmer
Inhibit NO production via down regulation of eNO
Neutrophils
↑Adhesion on activated endothelial cells
↑IL-8 expression
↑Induce proinflammatory cytokine release
(IL-6, TNF-α)

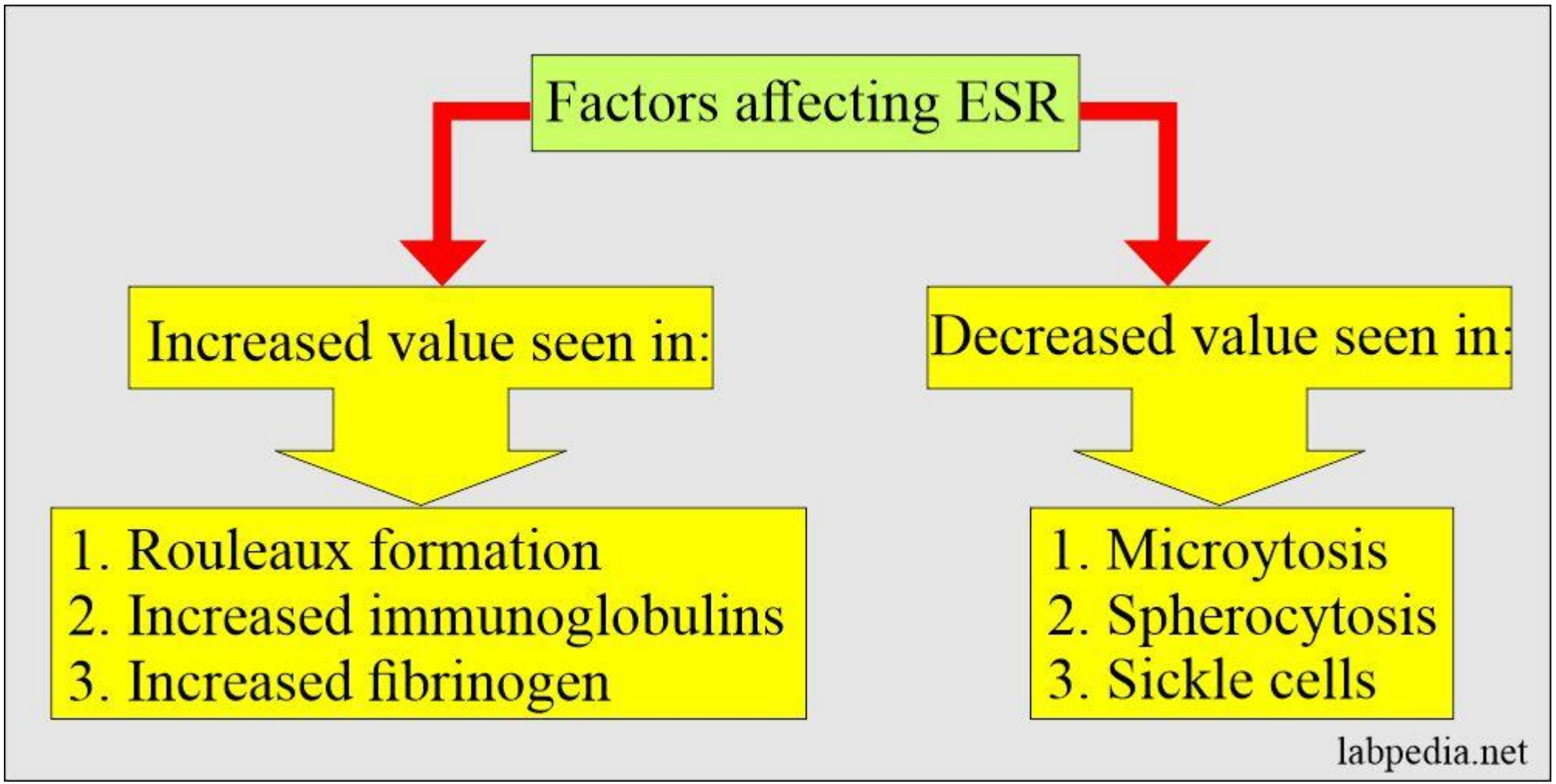

ESR
normal
abnormal
0
20-30


CRP
Induces complement activation
Increases LDL uptake & oxidation
Inhibits nitric oxide production
Induces production of tissue factor
Upregulates the expression of adhesion molecules
Inhibits fibrinolysis by increasing expression of PAI-1
Facilitates infiltration of monocytes into the vessel wall

2. Discordant Values in Hospitalized Patients

ESR/Low CRP	High CRP/Low ESR
ections (Bone and joint)	• Infections (urinary tract, gastrointestinal tract, lung and bloodstream)
nnective tissue disease (SLE)	• Myocardial infarction
hemic stroke	• Venothromboembolic disease
lignancy	• Rheumatoid arthritis
nal insufficiency	• Low serum albumin
v serum albumin	

viations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SLE, mic lupus erythematosus.


Factors affecting ESR
Increased value seen in:
1. Rouleaux formation
2. Increased immunoglobulins
3. Increased fibrinogen
Decreased value seen in:
1. Microytosis
2. Spherocytosis
3. Sickle cells
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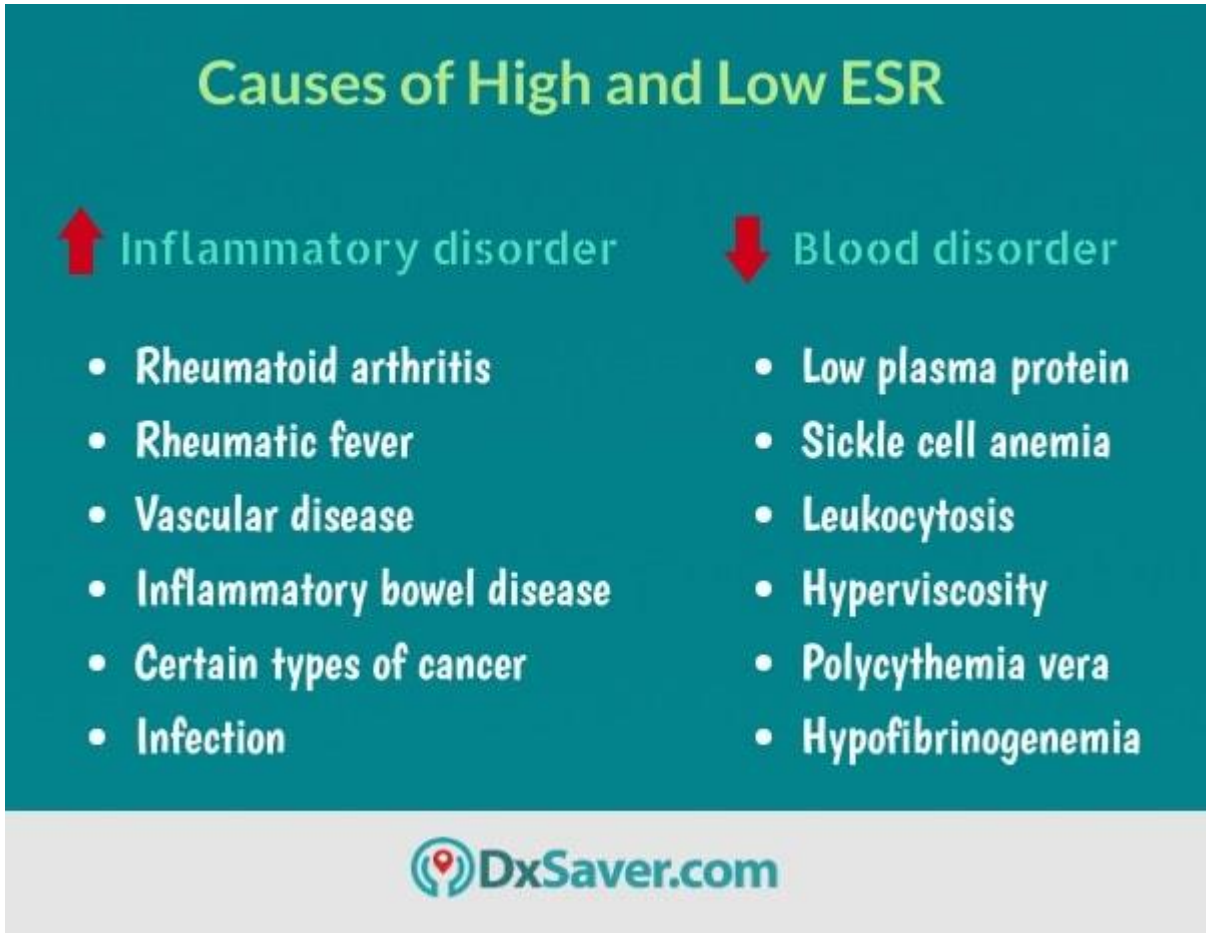

Causes of High and Low ESR
Inflammatory disorder
Rheumatoid arthritis
Rheumatic fever
Vascular disease
Inflammatory bowel disease
Certain types of cancer
Infection
Blood disorder
Low plasma protein
Sickle cell anemia
Leukocytosis
Hyperviscosity
Polycythemia vera
Hypofibrinogenemia
DxSaver.com

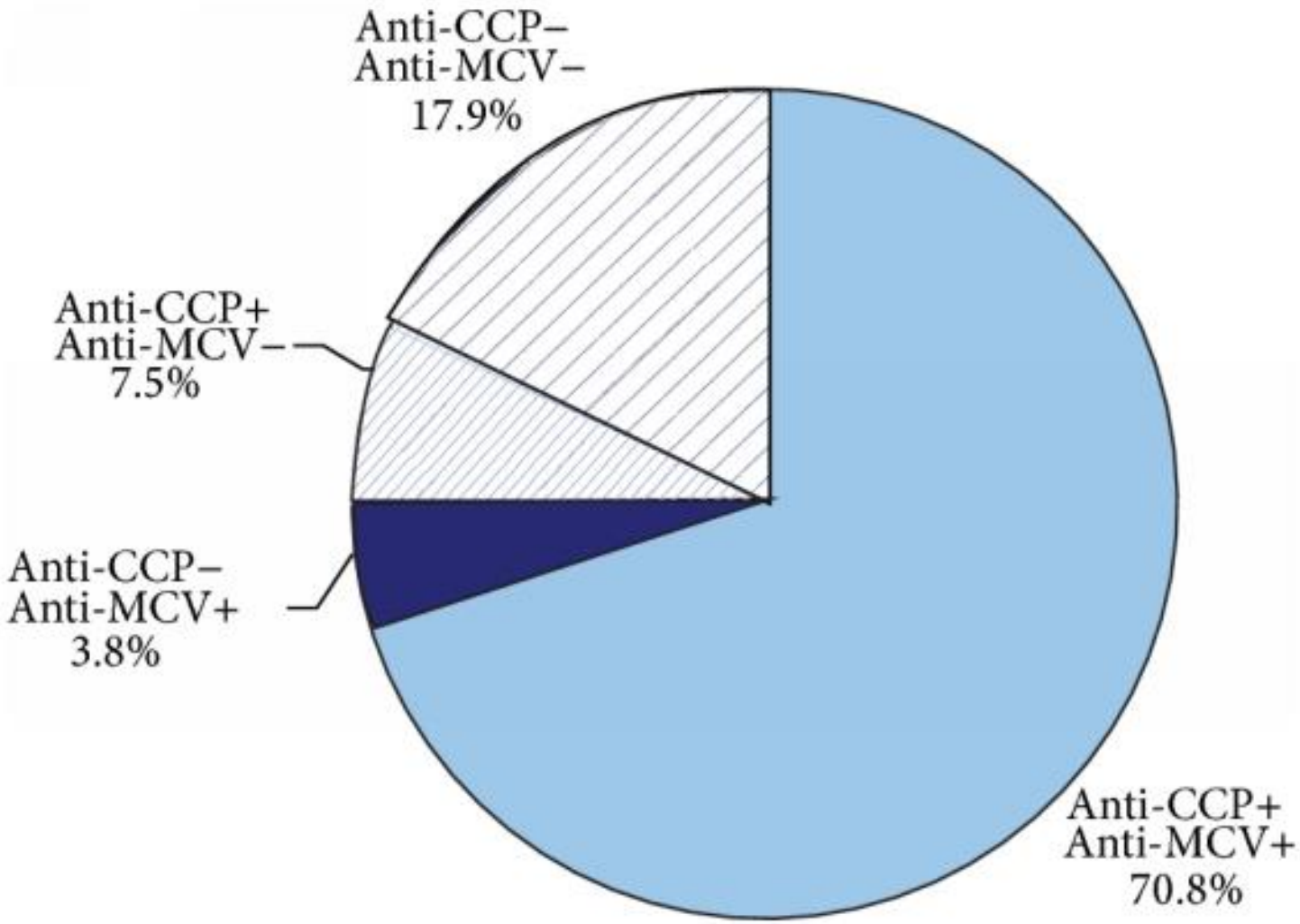
Causes of High (> 100 mm/hr) ESR

- Acute bacterial infections
  - Meningitis
  - Pneumonia
  - Cholangitis
  - Septic arthritis
  - Osteomyelitis
  - Pyelonephritis
  - Abscesses
- Polymyalgia rheumatica
- Rheumatoid arthritis
- S.L.E.
- Viral encephalitis
- Multiple myeloma
- Leukemia
- Lymphoma
- Carcinomas
- Drug hypersensitivity reactions
- Pulmonary infarction
- Uremia
- Open heart surgery
- Cerebrovascular accident
- Thrombophlebitis
- Major orthopedic surgery

Fever With Nonspecific Laboratory Finding

Fever and ESR > 100 mm/hr

- Sepsis
- Abscess
- TB
- Osteomyelitis
- Infective endocarditis
- Kala azar
- Lymphoma
- Leukemia
- Collagen vascular diseases
- Multiple myeloma
- Subacute thyroiditis


Anti-CCP–
Anti-MCV–
17.9%
Anti-CCP+
Anti-MCV–
7.5%
Anti-CCP–
Anti-MCV+
3.8%
Anti-CCP+
Anti-MCV+
70.8%

RF TEST

A negative (normal) result means that you have little or no rheumatoid factor in your blood. But that doesn't rule out rheumatoid arthritis or another health problem.

Many people with rheumatoid arthritis have little or no rheumatoid factor.

Can RF be negative and then positive?

Your rheumatoid arthritis markers may change over time from negative to positive, since many people with seronegative rheumatoid arthritis begin to develop RF or ACPA antibodies. “It happens, but it's not that common,”

Can you have a negative RF but positive anti-CCP?

Moreover, studies have shown that anti-CCP is positive even in those RA patients who are RF negative. This shows that anti-CCP should ideally be used as first line investigation in RA patients.

Is RF always positive in rheumatoid arthritis?

Many people with rheumatoid arthritis or Sjögren syndrome have positive RF tests. The higher the level, the more likely one of these conditions is present. There are also other tests that can be done to help make the diagnosis. Not everyone with a higher level of RF has rheumatoid arthritis or Sjögren syndrome.

Can RF be false negative?

False-negative and false-positive results are common in patients without RA, as well as those with RA; patients without RA have an 8% rate of false results, whereas patients with RA have a 15% rate.

Is RA positive or negative?

Some healthy people test positive for anti-CCPs, while others who have RA have negative test results. Blood tests are just one of several factors, including a medical history, physical exam and X-rays, that help doctors diagnose the disease.

What is the most specific test for rheumatoid arthritis?

Magnetic resonance imaging (MRI) and ultrasound may help diagnose rheumatoid arthritis in the early stages of the disease. In addition, these imaging tests can help evaluate the amount of damage in the joints and the severity of the disease.

Which is the more accurate test for diagnosis of RA?

Anti-CCP antibody test (ACCP or CCP). This test is for a type of autoantibody called cyclic citrullinated peptide (CCP) antibodies, which can be found in the blood of 60% to 80% of people with rheumatoid arthritis.

Can anti-CCP be negative in rheumatoid arthritis?

A positive anti-CCP result means RA is likely
but a negative result does not rule out RA.

Is RF positive in lupus?

Rheumatoid factor (RF) is found commonly in patients with systemic lupus erythematosus (SLE), and has been associated with a more benign disease course.

Does rheumatoid factor fluctuate?

Anticitrullinated protein antibodies and rheumatoid factor fluctuate in early inflammatory arthritis and do not predict clinical outcomes.

What is Anti-MCV test?

Anti-MCV® is an ELISA test for the quantitative determination of IgG antibodies against mutated citrullinated vimentin (MCV) in human serum or plasma. It is a powerful serological test for rheumatoid arthritis, especially in early disease.

What is the full form of Anti-MCV antibody?

Objectives: To evaluates the diagnostic performance of the anti-CCP2, anti-CCP3 and anti-mutated citrullinated vimentin (anti-MCV) tests in differentiating rheumatoid arthritis (RA) from other forms of arthritis in a clinical setting of early arthritis.

Conditions associated with rheumatoid factor

Condition	Frequency
Rheumatoid arthritis	70%
Other autoimmune rheumatic conditions	
Primary Sjögren syndrome	75%–95%
Systemic lupus erythematosus	15%–35%
Systemic sclerosis	20%–35%
Systemic vasculitis	5%–20%
Infections[a]	
Infective endocarditis	40%
Syphilis	8%–37%
Hepatitis B	25%
Hepatitis C	76%
Human immunodeficiency virus infection	10%–20%
Tuberculosis	15%
Other diseases	
Liver cirrhosis	25%
Mixed cryoglobulinemia	100%
Primary biliary cirrhosis	45%–70%
Healthy people	5%–25%[b]

[a]The rheumatoid factor in infectious diseases is produced by B cells, possibly to clear the immune complexes. They are usually transient and harmless.

[b]The frequency rises with age (5% at age 50, rising to 10% to 25% at age 70.

Data from reference 3.