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CLINICAL UTILITY OF ESR AND CRP: A SYSTEMATIC LITERATURE REVIEW

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Abstract:

Background: *Erythrocyte Sedimentation Rate (ESR) and C - reactive protein (CRP) are markers for acute phase reaction used for general screening, diagnostic purpose and assessing response to treatment. ESR is the rate of sedimentation of RBCs if a column of anti-coagulated fresh blood is left to stand, undisturbed for an hour. CRP is pentameric protein of hepatic origin that increases interleukin secretions by macrophages and t- cells. For measuring erythrocyte sedimentation rate two methods are used in which commonly used is Westergren method. The C - reactive protein test is based on the principle of the latex agglutination commonly done by two ways, Qualitative Test and Semi-Quantitative Test.*

Methods: *Peer reviewed research papers from different search engines are considered with the help of keywords. After primary scrutiny, those having the clinical utility are included. Total 22 research papers are included in the study.*

Discussion: *ESR and CRP are markers of acute phase reaction used clinically for diagnosis and monitoring of inflammatory condition. Raised ESR reflects increased plasma protein/ fibrinogen level whereas increased CRP is reflective of underlying inflammation. These markers are helpful in distinguishing the functional disorders from organic pathology.*

Conclusion: *Both ESR and CRP are commonest acute phase markers but clinically ESR has more utility in infective diseases whereas CRP is more prone to rise in inflammatory condition. Therefore, both markers should be used judiciously.*

Keywords: *Erythrocyte Sedimentation Rate (ESR), C - reactive protein (CRP), Cytokines, Inflammation, Infection.*

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INTRODUCTION:

The Erythrocyte Sedimentation Rate (ESR or Sed rate) and C-reactive protein (CRP) are used to detect inflammation (acute or chronic) in the body and are among the oldest laboratory tests (Vajpayee et.al 2011), (Tillett et.al., 1930), (Clyne, et. al. 1999), (Peppy, et. al.,2003), (Park et. al., 2010), (Wolfe, 1488), (Brigden, 1999). Both these tests are widely used for general screening, diagnostic purpose and assessing response to the given treatment.

ESR test sometimes referred as the Fåhraeus-Westergren test, it measures the distance through which erythrocytes fall within 1 hour in a vertical tube of anticoagulated blood. Its significance was first reported by Dr. Edmund Faustyn Biernacki in 1897. Westergren defined standards for the performance of the ESR test (Brigden,1999) (Grzybowiska et.al. 2011).

The ESR rate increases as a result of any cause or focus of inflammation. When an inflammatory process is present, fibrinogen enters the blood in high amounts and causes red cells to stick to each other, which raises the ESR. (Vajpayee et. al., 2011) Moderate elevations are common in active inflammatory diseases. (Vajpayee et. al., 2011), (Tillett et. al., 1930). But because the test is often normal in patients with neoplasm, connective tissue diseases, and infection; a normal ESR cannot be used to exclude these diagnostic possibilities.(Janson, et.al., 2012)

Method for measuring ESR (Hirsch,2017), (Erythrocyte sedimentation rate, 2018), (Sed rate, 2017)

For measuring erythrocyte sedimentation rate two methods are used, Westergren method, and Wintrobe method. Most commonly used method is Westergren method. In this method Westergren-Katz tube is filled with blood, until the blood level reaches 200 millimeters (mm).The tube should be stored vertically and sit at room temperature for an hour. Then measure the distance between the top of the blood mixture and the top of the sedimentation of RBCs.

The following are considered normal ESR test results: (Hirsch,2017), (Erythrocyte sedimentation rate,2018), (ESR, 2018), (Sed rate, 2017)

- Women under age 50 should have an ESR under 20 mm/hr.
- Men under age 50 should have an ESR under 15 mm/hr.
- Women over age 50 should have an ESR under 30 mm/hr.
- Men over age 50 should have an ESR under 20 mm/hr.
- Newborns should have an ESR under 2 mm/hr.

Table 1: Different conditions of ESR variations (Hirsch,2017), (Erythrocyte sedimentation rate, 2018), (ESR, 2018), (Sed rate, 2017)

High ESR	Higher than normal	Low ESR
Anemia	Systemic Lupus Erythematosus	Congestive Heart Failure
Kidney Disease	Rheumatoid Arthritis	Hypofibrinogenemia
Lymphoma	Giant Cell Arteritis	Leukocytosis
Multiple Myeloma	Polymyalgia Rheumatica	Low Plasma Protein
Old Age	Primary Macroglobulinemia	Polycythemia
Pregnancy	Too Much Fibrinogen In Blood, Or Hyperfibrinogenemia	Sickle Cell Anemia
Temporal Arteritis	Allergic Or Necrotizing Vasculitis	
Thyroid Disease	Infection (Bone Infection, Heart Infection ,Heart Valve Infection, Rheumatic Fever, Skin Infection, Systemic Infection, Tuberculosis)	
Waldenstrom's Macroglobulinemia		
Certain Types Of Arthritis		

C-Reactive Protein (CRP) was first discovered in 1930 by Tillet and Francis during their serologic studies of patients with pneumococcal pneumonia (Tillett et. al., 1930). The protein was so named because it binds to the C-polysaccharide of the pneumococcus. It was found later that the protein appeared in plasma during many infectious or inflammatory conditions (Clyne, et. al. 1999), (Peppy, et. al.,2003), (Park et. al., 2010), synthesis of CRP occurs in the liver and is stimulated by the presence of cytokines, particularly interleukin, IL-1 beta, IL-6, and tumor necrosis factor (TNF) (Jaye, et. al., 1997).

The physiological role of CRP is to bind to phosphocholine expressed on the surface of dead or dying (apoptosis) cells in order to activate the complement/immune system, which enhances phagocytosis by macrophages. Levels of CRP begin to rise within 2 hours of an insult, and have a half-life of about 18 hours. The rapid action of CRP makes it a participant in the acute or first phase of the inflammatory process that is why it is often called an "acute-phase protein (Clyne, et. al. 1999), (Peppy, et. al., 2003).

CRP reading of greater than 10 mg/L is especially high and may indicate :- (Afshin et.al.,2015), (Block, et.al.,2009, (Cauci, et. al.,2008), (Effoe, et. al., 2015), (Emst,et, al., 2011), (Leuzzi, et. al.,2017), (Mazdi, et. al.,2017), (Neale, et. al.,2016), (Ridker, et. al.,1998), (Smidowicz, et. al., 2015)

- A bone infection, or osteomyelitis;
- An autoimmune arthritis flared-up;
- Inflammatory bowel disease (IBD);
- Tuberculosis;
- Lupus, connective tissue disease, or other autoimmune diseases;
- Cancer, especially lymphoma;
- Pneumonia or other significant infection.

Principle of CRP Test (Effoe, et. al., 2015), (Mazdi, et. al.,2017)

The C-Reactive Protein test is based on the principle of the latex agglutination. When latex particles complexed human anti-CRP are mixed with a patient's serum containing C-reactive proteins, a visible agglutination reaction will take place within 2 minutes.

Procedure of CRP Test (Effoe, et. al., 2015), (Mazdi, et. al.,2017)

For CRP to be done, commonly two ways are used which are as follows:

1. Qualitative Test

1. Bring all reagents and serum sample to room temperature and mix latex reagent gently prior to use. Do not dilute the controls and serum.
2. Place 1 drop of serum, positive control and negative control on separate reaction circle on glass slide.
3. Then add 1 drop of CRP latex reagent to each of the circles.
4. Mix with separate mixing sticks and spread the fluid over the entire area of the cell.
5. Tilt the slide back and forth slowly for 2 minutes observing preferably under artificial light.
6. Observe for visible agglutination.

2. Semi-Quantitative Test

1. Prepare dilution of the specimen with physiological saline 0.9%, as indicated in the following table 2.
2. Then proceed for each dilution as in qualitative test.

Table – 2 showing preparation of dilution of specimen with physiological saline 0.9%

Dilution	CRP (ug/ml) in undiluted sample
1:2	14
1:4	28
1:8	56
1:16	112
1:32	224
1:64	448

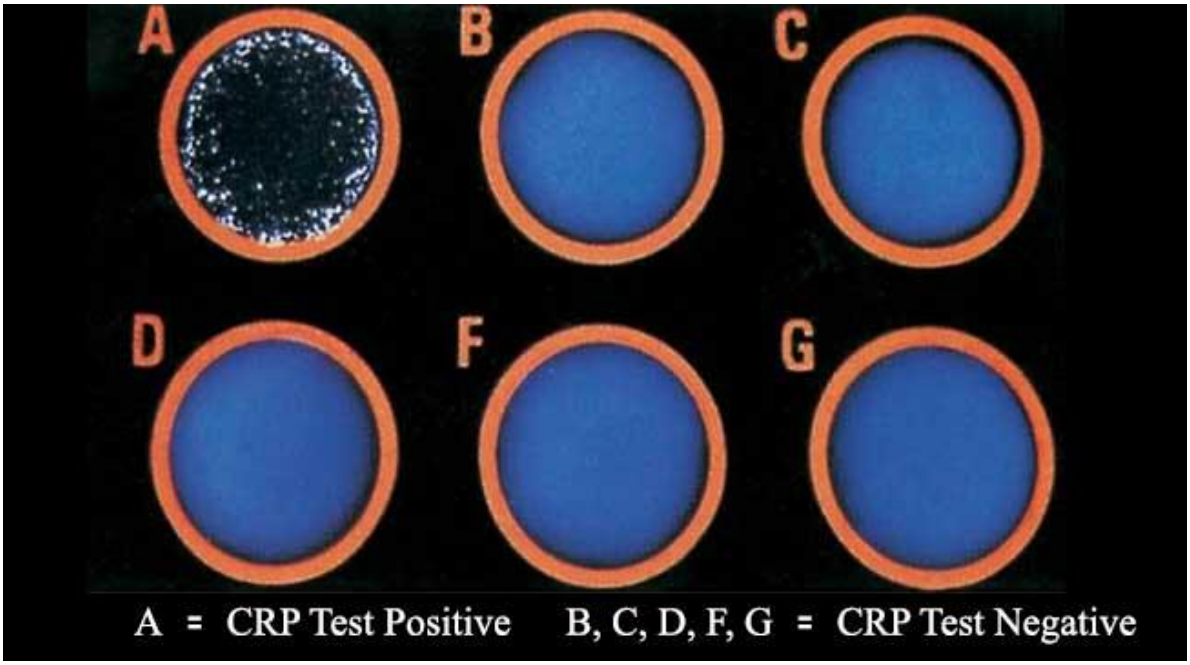

Figure 2: Result Interpretation of CRP Test (Aryal S., 2018)
Positive: Agglutination of latex particles, indicating the presence of C – reactive protein at a significant and detectable level.
Negative: No Agglutination.
For Semi-Quantitative Test Results, the last dilution of serum with visible agglutination is the CRP titre of the serum.
Calculation of titre:
CRP ug/ml = 7 x D, where D is the highest dilution of serum showing agglutination and 7 is the sensitivity in ug/ml.

METHODS:

Peer reviewed research papers from different search engines (Like PubMed, MedLine etc.) were searched with the help of keywords (ESR, CRP, ESR & CRP). The final list of the available research papers thoroughly scrutinized for final inclusion in the literature review. Those having the clinical utility were included for the study. Total 22 research papers are included in the study, including 8 web pages having the recent updates on issue. No timeline restriction was considered for the inclusion.

DISCUSSION & RESULT:

Clinical application of ESR and CRP— The acute phase reactants ESR and CRP are used clinically for diagnosis and monitoring of inflammatory conditions such as infections, trauma, infarction, neoplasm, inflammatory arthritis, and systemic autoimmune disease. ESR and CRP levels also may provide insight into the underlying disease process. Elevations in ESR reflect disease states that involve increased plasma protein/fibrinogen levels such as autoimmune conditions or cardiovascular disease. Increased levels of CRP generally are reflective of underlying inflammation, such as that resulting from trauma or infection. In contrast, deceptively low CRP levels may be found in patients with infections caused by low virulence organisms or in those treated with antibiotics. In the case of functional disorders such as irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia, and somatic symptom disorders, a normal ESR and CRP may help to distinguish these conditions from organic pathology. (Katz, et. al., 1989)

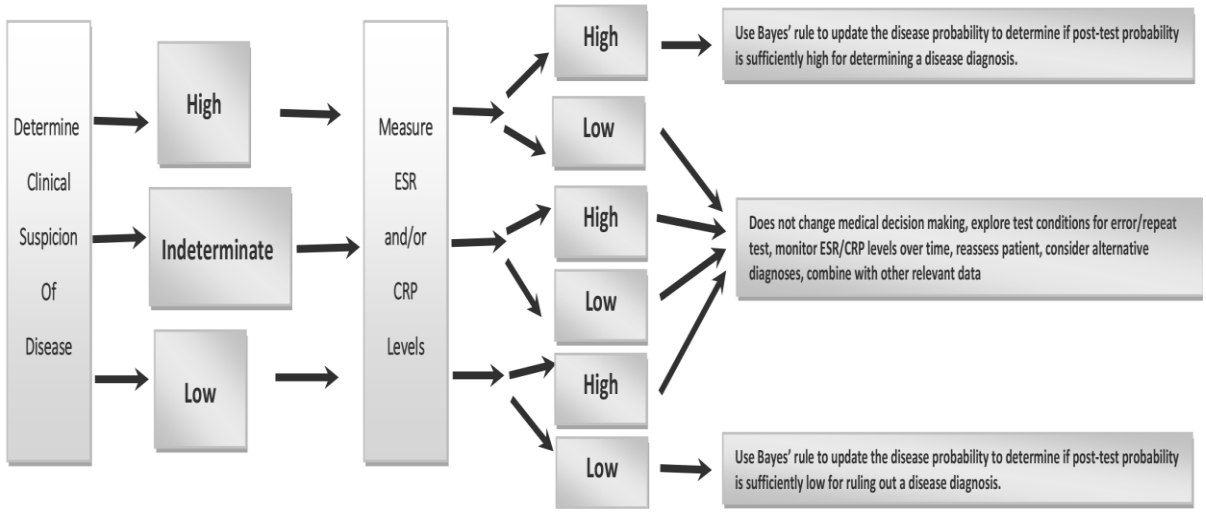

Figure 2: Utilization of ESR and/or CPR Tests to aid in clinical decision making (Christopher et .al., 2011)

Bayes' rule is a way to figure out conditional probability. Conditional probability is the probability of an event happening, given that it has some relationship to one or more other events. For example, your probability of getting a parking space is connected to the time of day you park, where you park, and what conventions are going on at any time. Bayes' theorem is slightly more nuanced. In a nutshell, it gives you the actual probability of an **event** given information about **tests**.

- "Events" are different from "tests." For example, there is a **test** for liver disease, but that's separate from the **event** of actually having liver disease.
- **Tests are flawed**: just because you have a positive test does not mean you actually have the disease. Many tests have a high false positive rate. **Rare events tend to have higher false positive rates** than more common events. We're not just talking about medical tests here. For example, spam filtering can have high false positive rates. Bayes' theorem takes the test results and calculates your *real probability* that the test has identified the event.

Bayes' Theorem (also known as Bayes' rule) is a deceptively simple formula used to calculate conditional probability. The Theorem was named after English mathematician Thomas Bayes (1701-1761). The formal definition for the rule is:

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

Table 3 :Basic Difference Between ESR and CRP (Christopher et .al. , 2011)**, (**Singh et. al., 2018).

Laboratory Test	Levels	Interpretation	Cause
ESR	• Normal: men 3 mm/h and women 7mm/h • Rates increase with age	An anti - inflammatory focus has been present for at least several days somewhere in the body, including CNS	Fibrinogen levels go up in the serum, which causes red cells to clump
hs-CRP	Normal < 1mg/l	Elevated CRP indications an active inflammation somewhere in the body, including the CNS. It has caused cellular death and dying within the past 24 hours	Dead and dying cells release chemical factors, which cause the liver to produce CRP
Abbreviations:CNS, central nervous system; hs- CRP, highly sensitive C- reactive protein; ESR, erythrocyte sedimentation rate			

Table 4: Discordant Values in Hospitalized Patients (Christopher et .al. , 2011)**, (**Singh et. al., 2018).

High ESR/Low CRP	**High CRP/Low ESR**
Infections (Bone and joint)	Infections (urinary tract, gastrointestinal
Connective tissue disease (SLE) tract	lung and bloodstream
Ischemic stroke	Myocardial infarction
Malignancy	Venothromboembolic disease
Renal insufficiency	Rheumatoid arthritis
Low serum albumin	Low serum albumin
Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SLE,systemic lupus erythematosus	

CONCLUSION:

The modern clinical utility of the aforesaid investigation is to be studied with modern research methods and larger sample size to evaluate the significance. Both ESR and CRP are commonest acute phase markers but clinically ESR has more utility in infective diseases whereas CRP is more prone to rise in inflammatory condition. Therefore, both markers should be used judiciously.

Recommendations for future researches – Future research should be focused on diagnostic utility of CRP related to ESR within same population. Studies should be done on elderly people to clarify whether it has any distinct advantage on ESR in the day to day clinical practice.

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