Erythrocyte sedimentation rate and C-reactive protein: Effective tests of inflammation

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Inflammatory Markers

Inflammatory markers are usually determined as part of the initial laboratory screening of patients suspected of having acute inflammation caused by an underlying specific disease or condition.[1] Erythrocyte sedimentation rate (ESR) is a widely used test, useful as a general indicator of inflammation.[2] In addition to a screening test, it is performed routinely to monitor patients for autoimmune and infectious diseases.[2] The sedimentation rate of patient samples helps determine the severity of inflammation and whether treatment is effective.[3] ESR is commonly performed when there is a suspicion of inflammatory conditions, and can be elevated in systemic infections, orthopedic infections, bronchiolitis, giant cell arteritis, kidney, coronary, and autoimmune diseases, vasculitis, and certain cancers, among other conditions.[3-5]

C-reactive protein (CRP) is another widely used serological biomarker of systemic inflammation. In addition to inflammation, this protein is part of the immune system's reaction to bacterial and fungal infections, autoimmune disorders and cardiovascular diseases.[6] Because CRP increases more significantly with bacterial as opposed to viral infections, it can also help a clinician determine if antibiotics are warranted.[7] ESR and CRP are the most widely used tests for initial screening of inflammatory conditions.[8]

Clinical Use of ESR and CRP

ESR and CRP are nonspecific screening tests and therefore lack both sensitivity and specificity, and neither should be used by itself to diagnose infectious or inflammatory disorders[9], nor should low or normal values exclude a diagnosis made clinically.[10] Both are useful as adjuncts in the diagnosis and monitoring of both acute and chronic inflammatory conditions such as trauma, infection, infarction, neoplasm, and systemic autoimmune diseases including inflammatory arthritis.[10] Their greatest utility comes perhaps when there is high or low clinical probability of disease. A low ESR/CRP in a patient with a low clinical suspicion of disease may further lower the post-test probability of disease.[10] A high ESR or CRP in a patient with a high suspicion of disease may increase post-test probability and aid in definitive diagnosis.[10] A retrospective cohort study showed discrepancy between ESR and CRP in 12.5% of patients.[11] These discrepancies may be due to acute phase timing, where CRP rises before ESR in inflammation, but can also be seen in instances of ESR increase with a normal CRP, frequently found in malignancies and other non-inflammatory conditions.[12] Utilizing both tests may provide needed diagnostic information.

Dual Marker Use Cases

CRP levels are proportional to the intensity of inflammation and sensitive to subtle changes in acute responses.[1,12-13] Therefore, CRP is often the preferred biomarker for acute inflammatory conditions. Because of its short half-life and rapid kinetics, CRP falls rapidly once inflammation resolves so it is also useful as a measure of response to treatment.[10,14] After age 40, there is an age-related elevation of ESR, especially after age 60.[14] CRP is also affected by age, but to a much lesser extent.[14] Renal disease and female gender also increase ESR.[12] High ESR/low CRP can help detect low-grade bone

infection and is useful in monitoring some patients with systemic lupus erythematosus.[12] Of cardiovascular relevance, individuals with high ESR/low CRP are more frequently diagnosed with ischemic stroke or transient ischemic attack, while low ESR/high CRP is more likely seen in myocardial infarction and venous thromboembolism.[11]

Multiple studies have shown a positive correlation between elevated ESR and CRP levels compared to radiographic and functional outcomes in patients with rheumatoid arthritis (RA).[15-16] Elevated ESR has proven to be a better predictor of patient outcomes in the early stages of RA, while CRP may be superior to ESR in later stages of the disease.[15] ESR and CRP have similar diagnostic accuracy in the assessment of acute orthopedic inflammation.[17] Although lacking in specificity, Both ESR and CRP measurements continue to be important in the diagnosis and management of RA.[18]

Elevated ESR with CRP improves sensitivity and specificity over either ESR or CRP alone. In a meta-analysis of four periprosthetic infections the relative sensitivity of combined markers over ESR alone was 0.95 (95% CI, 0.90-1.00; P = 0.063) and 0.94 (95% CI, 0.89-0.99; P = 0.027) for CRP.[4] Specificity was 1.21 (95% CI, 1.13-1.30; P < 0.001) for the combination vs. ESR and 1.16 (95% CI, 1.09-1.25; P < 0.001) for CRP.[4] In an analysis of two studies of pediatric orthopedic infections, combination of ESR + CRP improved relative overall diagnostic accuracy over ESR alone 1.31 (95% CI, 1.19-1.45; P < 0.001).[4] One study on giant cell arteritis found that ESR + CRP to increase overall diagnostic accuracy over ESR alone (P = 0.001) and CRP alone (P = 0.004).[19]

ESR Method and Marker Assay Turnaround Times

Introduced in 1921 and recommended by the International Council for Standardization in Hematology (ICSH), the Westergren ESR test is a widely-used, manual method which measures the sedimentation rate of blood cells in a test tube over one hour.[2,20] In adults, the normal ESR range is < 15 mm/hr in males under 50, < 20 mm/hr in males over 50, < 20 mm/hr in females under 50, and < 30 mm/hr in females over 50.[21]

While a long-standing test, this method has been described as tedious, its results are operator-dependent with lengthy turn-around-times (TATs), standardization and quality control issues. ESR testing has become much more convenient with the advent of automated systems conducted at point-of-care (POC) or near-patient.[3] In a 2019 abstract for the *American Journal of Clinical Pathology*, researchers found TAT decreased when using an automated ESR method (3 minutes for the first specimen then 15-20 seconds for each sequential specimen) when compared to the Westergren (1 hour per specimen).[22] As a result of readily available automated devices, in 2017, the ICSH released recommendations for emerging automated ESR methodologies.[23] The Westergren method remained the reference method for ESR; all new technologies were to be evaluated against the reference prior to use in the clinical lab.

Only marginally younger in age, CRP was discovered in 1930, and CRP assays have since undergone a similar range of developmental milestones.[24] Originally high-complexity assays, recent developments have included high-sensitivity assays and novel POC devices. Similar again to ESR, it should be noted that POC CRP assays show variability over high-level CRP concentrations compared to routinely used central laboratory methods.[25] Published studies suggest that high-level CRP should be verified by a central laboratory assays, which may be run in one hour, but are often batched and have a turnaround time of 24 hours or more.[25]

Cost Effectiveness of ESR and CRP

Modified Westergren patient/payor costs range between $28.00 and $69.00, while CRP tests cost between $48.00 to $199.00. However, patient/payor costs can vary dramatically between laboratories, providers, test methods, and cash vs. insurance pricing. Per assay cost for laboratories have a better correlation to reimbursement costs by CPT code. The CPT codes and respective reimbursement rates are CPT 85651 ($4.27) and 85652 ($2.70) for ESR and 86140 ($5.18) for standard screening CRP and 86141 ($12.95) for high sensitivity CRP. An automated ESR system can produce a result for as little as ~$2.00 per test cost to the laboratory. Automated ESR has been shown to be cost effective at an on-site hospital laboratory where physicians frequently utilized ESR testing in the inpatient, outpatient, and emergency

department settings as part of infection workup and other workups for autoimmune disorders, neurology disorders, and ophthalmology issues.[3] They stated that most commercial ESR analyzers are fairly inexpensive and, in some cases, the analyzer can be acquired for little or no upfront costs when bundled with a signed commitment for particular purchase levels.[3] These 'kits' reduce the variation between operators/laboratories and enhance the standardization of results. Because blood and anything it contacts is potentially infectious, automated procedures reduce exposure by providing fewer transfers and the use of sealed, throw-away consumables. ESR is mentioned in the list of "top 25 tests by volume" from numerous hospital surveys performed in five different countries.[26]

Automated ESR analyzers have been shown in peer-reviewed literature, published reports, and in-house studies by manufacturers to improve laboratory efficiencies—notably workflow, ease of use, and TATs. Training time for laboratory technicians is reduced compared to complicated manual procedures. Automated ESR analyzers employ user-friendly kits, pre-made standards, reagents, and consumables which reduce 'hands-on' bench time. ALCOR Scientific performed a comparison of turnaround time and workflow efficiencies between the Westergren reference method and iSED/iSED ELITE. Compared to 81.9 minutes with the manual Westergren method, the iSED requires 10.3 minutes for a run of 20 samples. The hands-on time needed for technician manipulation is also reduced ≤ 1 minute versus 23.5 minutes for the Westergren. In a 2019 abstract for the *American Journal of Clinical Pathology*, researchers found TAT decreased when using the ALCOR iSED (3 minutes for the first specimen due to onboard mixing then 15-20 seconds for each sequential specimen) when compared to the Westergren (1 hour).[22]

Despite its long history of use and non-specificity, it is evident that while CRP may be readily used for acute inflammation, ESR will not disappear from clinical practice.[8,26] When combined with CRP, patient history and clinical symptoms ESR remains a useful low-cost parameter for multiple diagnoses and provides information unavailable from CRP testing alone.

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