Clinical Utility of the Erythrocyte Sedimentation Rate: A Case Study

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ABSTRACT

The Erythrocyte Sedimentation Rate (ESR) is a laboratory test of historical significance and broad applicability. Its current role in medical diagnostics, however, is often debated due to a lack of specificity in the results and the emergence of more up-to-date alternatives. This case study, however, illustrates a clinical scenario where the ESR was utilized on more than one occasion to significantly aid the diagnostic process and ultimately, improve patient care.

ABBREVIATIONS: ESR, Erythrocyte Sedimentation Rate; CBC, complete blood count; WBC, white blood cell; MS, Multiple Sclerosis; RBC, red blood cell; PID, pelvic inflammatory disease; RA, rheumatoid arthritis; CRP, C-reactive protein

INDEX TERMS: Erythrocyte Sedimentation Rate (ESR); clinical utility; case study; multiple sclerosis

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INTRODUCTION

Historically, the Erythrocyte Sedimentation Rate (ESR) has been a commonly ordered laboratory test utilized as a screen for non-specific inflammation. However, because the ESR result is reflective of a generalized process rather than a specific analyte, its clinical and diagnostic utility have often been debated.[1-4] Further scrutiny of the value of the ESR has evolved recently as new and more specific laboratory techniques have been developed.[5] Despite these questions, the following case will highlight the current clinical importance of the ESR—one that can save time, money, and most importantly, lead to improved patient care.

CASE STUDY

An overweight, 29-year-old Caucasian male presented to a rural family medical clinic with the chief complaint of bilateral numbness in his legs for the past week. The patient reported that the numbness/tingling sensation started at his waistline and radiated to "everything below the belt". The numbness was constant, with nothing seeming to improve or worsen the feeling. The patient denied any history of diabetes, back pain, and/or neck pain.

Upon examination, the patient did not appear to be in distress and a complete review of systems was negative, with the exception of numbness and tingling in the lower extremities. Vital signs were also normal with a blood pressure of 120/80, temperature of 96.3°F, 16 respirations per minute, and a pulse of 68 beats per minute. Cardiovascular, pulmonary, and musculoskeletal examinations were all grossly within normal limits. However, the neurological examination revealed diminished patellar reflexes bilaterally, and decreased sensation to light and sharp touch from the waist down.

After the patient's history and physical examination were complete, the following laboratory tests were ordered: complete blood count (CBC) with white blood cell (WBC) differential, ESR, and a basic metabolic panel. With the exception of a mildly elevated ESR, all laboratory results were within normal reference limits. A summary of these results can be found in Table 1.

Based on laboratory results, a diagnosis of diabetes mellitus was ruled out. With the elevated ESR

suggesting some sort of abnormal process, and few diagnostic options remaining to explain the symptoms in this otherwise healthy male, the clinician proceeded with a MRI of the lumbar spine. The MRI showed a possible presacral lesion suspicious for a mass, and consequently the patient was referred for neurology consult.

Table 1. Summary of Initial Laboratory Results

Test Parameter (units)	Patient (flag)	Reference Interval
WBC Count (x 10^3/μL)	10.3	4.8-10.8
RBC Count (x 10^{12}/L)	5.30	4.70-6.10
Hemoglobin (g/dL)	15.2	14.0-18.0
Hematocrit (%)	45.8	36.0-48.0
RDW-CV (%)	12.8	11.5-14.5
Platelet Count (x 10^3/μL)	252	130-400
Segmented Neutrophils		
Relative (%)	57	37-80
Absolute (x 10^3/μL)	5.9	1.8-8.6
Lymphocytes		
Relative (%)	32	10-50
Absolute (x 10^3/μL)	3.3	0.5-5.4
Monocytes		
Relative (%)	8	0-12
Absolute (x 10^3/μL)	0.8	0.0-1.3
Eosinophils		
Relative (%)	2	0-7
Absolute (x 10^3/μL)	0.2	0.0-0.8
Basophils		
Relative (%)	1	0-3
Absolute (x 10^3/μL)	0.1	0.0-0.3
ESR (mm/hr)	31 (↑)	0-15
Glucose (mg/dL)	99	70-100
BUN (mg/dL)	12	9-20
Creatinine (mg/dL)	1.00	0.80-1.50
Sodium (meq/L)	144	137-145
Potassium (meq/L)	4.4	3.5-5.1
Chloride (meq/L)	106	98-107
CO2 (meq/L)	25	22-30
Calcium (mg/dL)	9.9	8.4-10.3

At the time of consult, the patient's numbness had reportedly subsided and the neurological deficit present did not correlate with the level of the spine affected. As a result of this discrepancy further imaging of the spine was ordered, and revealed a mild disc protrusion but no masses or other abnormalities. Neurology notes stated that such findings could represent the effects of Guillain-Barré Syndrome. Because the patient's symptoms had improved, an additional ESR was performed to verify that the result had returned to within normal limits. The repeat ESR result remained elevated, however, prompting the neurologist to order a MRI scan of the brain. When this scan exposed several demyelinating plaques, the patient was definitively diagnosed with multiple sclerosis (MS).

DISCUSSION

Background of the ESR

The ESR is a laboratory test that measures the distance of erythrocyte settling per 60 minutes. Erythrocytes settle, or fall, out of their plasma solution as they aggregate. This happens in three distinct phases: 1) the aggregation phase; 2) the sedimentation phase; and 3) the packing phase.[6] In phase 1, the erythrocytes form rouleaux—a specific type of red blood cell (RBC) stacking where the cells take on a 'roll of coins' configuration. During phase 2, the RBCs continue to aggregate and eventually begin to fall out of solution. Finally, in phase 3, the RBC aggregates that have fallen out of solution become packed as they settle in the bottom of the testing tube.

The rate at which RBCs settle can be impacted by a number of factors. Increased amounts of plasma proteins such as fibrinogen or gamma globulins counteract the natural repellent zeta potential of erythrocytes, causing them to be forced closer together than normal.[6,7] As a result, the RBCs are more prone to rouleaux formation, which increases the rate at which they settle, thus leading to an elevated ESR result. Erythrocyte size and shape can also alter the settling rate. Macrocytic RBCs settle faster due to an increased surface-to-volume ratio, while microcytic RBCs tend to settle slower.[2,6] Because their altered shape impedes rouleaux formation, the presence of RBC poikilocytes such as spherocytes or dacryocytes leads to a decreased ESR value.[2,6,7] RBC settling is also affected by the concentration of erythrocytes, in that polycythemic individuals have decreased ESR values while patients with anemia exhibit increased ESR values.[2] Other physiologic factors or technical error can influence ESR results as well.

The ESR test can be performed using the Westergren or the Wintrobe method. The modified Westergren procedure is the recommended technique by both the International Council for Standardization in Haematology[8] and the Clinical Laboratory Standards Institute,[9] and offers the advantage of better accuracy with extremely elevated ESRs due to the taller testing tube involved. In performing the modified Westergren ESR, EDTA anticoagulated blood is mixed with diluent—most often sodium citrate—and used to fill a

200 mm tube, or test column. The test column is then placed vertically in a rack and left undisturbed for 60 minutes. After the 60 minute time interval has expired, the ESR result is determined by interpreting the distance that corresponds with the top of the RBC layer, as illustrated in Figure 1.

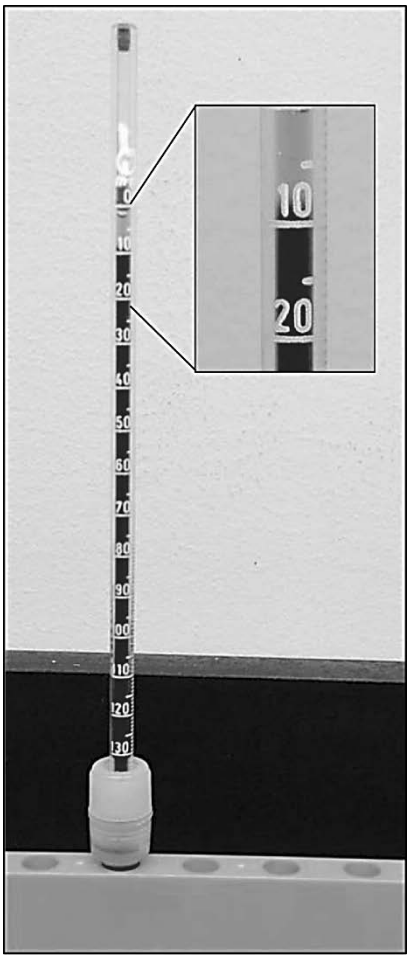

Figure 1. An ESR test. Determining the result is accomplished by interpreting the distance that corresponds with the top of the darker RBC layer. In this case, the ESR would be reported as ~8mm/hr (see inset).

This method is sensitive to technical errors that can lead to spurious results such as overfilling/underfilling the test column, not placing the test column exactly vertical, using inappropriate anticoagulants, or having air bubbles in the test column.[7] Automated ESR testing systems do exist, and can offer advantages such as shortened testing times, procedural standardization, and increased reproducibility.[6]

Establishing accepted reference intervals for the ESR has been somewhat challenging because of the influence of biological and other variables on testing results. In 1967, Böttiger and Svedberg performed a study in an attempt to solidify universal ESR result ranges. Findings from their study suggested that ESR reference intervals not only should account for the sex of the patient, but also his/her age,[10] as normal females had higher ESR results than males, as did individuals over the age of 50 when compared to those under the age of 50. Today's accepted ESR reference intervals, with slight variance from site to site, have remained close to those suggested by Böttiger and Svedberg, and are summarized in Table 2.

Table 2. Typical ESR Reference Intervals[6,7]

	Female	Male
0-50 years old	0-20 mm/hr	0-15 mm/hr
>50 years old	0-30 mm/hr	0-20 mm/hr

Clinical Utilization of the ESR

The ESR is a nonspecific test in that elevated results suggest the presence of tissue destruction and/or inflammation, but do not delineate the specific cause of those processes.[6] Elevated ESR results are known to be associated with many conditions where inflammation and/or tissue destruction occur, such as the examples listed in Table 3, and thus utilizing an ESR result alone for diagnostic purposes is futile and controversial. While the clinical role for the ESR continues to evolve and be debated, there does seem to be a consensus in the idea that the ESR is not a valuable tool for screening asymptomatic individuals.[3,5,12] However, because of its widespread availability, relative low cost, and non-invasive nature, the ESR can be a powerful tool in guiding decisions to pursue more costly and/or invasive procedures in symptomatic patients.[13]

The ESR result may also be of benefit in certain clinical scenarios when trying to differentiate between two conditions with similar patient presentation. For instance, when trying to distinguish unruptured appendicitis from pelvic inflammatory disease (PID), an elevated ESR is more indicative of the latter.[11] Another example of the discriminatory function of the ESR is in the discernment of iron deficiency anemia versus anemia of chronic disease in patients with coexisting chronic inflammatory conditions such as rheumatoid arthritis (RA). In otherwise healthy individuals, the

serum ferritin level is most often used to make this decision. However, in patients with underlying chronic inflammation, ferritin levels are falsely elevated because ferritin is an acute phase reactant. Thus, it has been suggested that ferritin levels in these individuals can be 'corrected' for the amount of inflammation present by factoring in the ESR result.[2,14]

Table 3. Conditions Known to Elevate ESR Results[6,11]

Acute coronary syndrome
Anemia
Collagen vascular disease
Diabetes
Infection
Inflammation (conditions associated with)
Multiple myeloma
Neoplasm
Nephrotic syndrome
Oral contraceptives
Osteomyelitis
Pelvic inflammatory disease
Polymyalgia rheumatic
Pregnancy
Pulmonary tuberculosis
Rheumatic fever
Rheumatoid arthritis
Subacute bacterial endocarditis
Systemic lupus erythematosus
Tissue destruction (conditions associated with)
Waldenstrom's macroglobulinemia

Historically, typical applications for the ESR were to gauge disease severity and monitor disease progression or response to treatment. For many of these conditions, more specific measures have since been developed to accomplish these tasks, but the ESR still remains advantageous in certain cases including RA, temporal arteritis, and polymyalgia rheumatic.[2,3] Particularly in the case of RA, present value of the ESR is evident in the fact that the American College of Rheumatology and European League Against Rheumatism developed 'Rheumatoid Arthritis Classification Criteria' includes analysis of ESR results,[15] as does the 28-joint Disease Activity Score.[16] That being said, according to recent studies, the C-reactive protein (CRP) assay may be gaining a slight preference advantage over the ESR for evaluating RA disease activity.[17,18] The ESR's predictive ability in estimating disease severity has been found to be of some value in additional clinical situations as well, such as cases of PID,[3,11] systemic lupus erythematosus,[19] and acute pancreatitis.[20]

Applications for the ESR in oncology have also been widely considered. Specifically, the ESR's role as a prognostic indicator, in estimating disease progression, and in the monitoring of therapy has been assessed. Typically, in conditions such as gastric carcinoma, chronic lymphocytic leukemia, breast cancer, etc., a poor overall prognosis has been found to correlate with elevated ESR values.[2] In Hodgkin Lymphoma, the ESR has been shown to be of value in monitoring response to therapy,[21,22] in that results remaining elevated following treatment indicate aggressive disease and poor prognosis.[23] Similarly, in patients with prostatic cancer, an elevated ESR correlates with increased risk of disease progression and mortality.[24] Recent studies have also suggested a link between ESR results and survival rates of patients with renal cell carcinoma.[25,26]

Utilization of the ESR as a 'sickness index' for elderly patients with nonspecific changes in health status and moderate likelihood of disease has also been proposed.[2,13,21] In such patients, a decline in health often indicates progression or development of a disease process. The ESR, when analyzed in conjunction with the clinical history, acts as a 'sickness index' that can guide clinical decision making.[13] Use of the ESR in this capacity may be limited due to the fact that results in the elderly are variable in relation to reference intervals.[27]

The non-specific nature of the ESR means that the list for its potential/studied clinical uses is significant, and new applications are continuously being proposed. For example, the role of inflammation in ischemic stroke has elicited hypotheses of the ESR as a prognostic indicator for that condition.[28] The obvious correlation between ESR results and inflammation/infection has brought forth studies of diagnostic and predictive value of the test in conditions such as giant cell arteritis,[29] diabetic osteomyelitis,[30] and mycosis fungoides.[31] Another interesting application of the ESR is in providing the patient and/or practitioner reassurance in cases of 'no pathology'.[32]

Current Case Applications

The current case study provides an excellent opportunity to dissect the value of the ESR in a real-life clinical scenario. This case is of particular interest because the ESR result impacted clinical decision making on two separate occasions. The first such

instance occurred upon initial patient presentation. The patient's symptoms seemed to be genuine and of concern, but all initial laboratory tests were normal—except the ESR. The elevated ESR indicated that some sort of abnormal process was occurring, which helped to rule-out psychosis or other benign causes. Although the ESR did not provide the practitioner with an exact diagnosis, it did give justifiable support for further testing. Had the ESR been normal, further testing likely would not have been pursued at that time.

The second occasion to witness the clinical utility of the ESR occurred later in the scenario, after a possible diagnosis of Guillain-Barré Syndrome had been identified. In this instance, an ESR had been ordered to confirm a return to normal levels, which would have correlated with the patient's symptoms and potential diagnosis. The ESR result, however, remained elevated. This discrepancy alerted practitioners of a possible misdiagnosis, and prompted further testing that did in fact reveal a very different and significant finding—MS.

In both instances of this case, an ESR result helped expedite the diagnostic process. Had the first and/or second ESR not been ordered, the patient's symptoms most likely would have been attributed to a condition such as sciatica in the case of the former, or Guillain-Barré Syndrome in the latter, and the underlying MS could have gone undiagnosed for months or even years. Identifying the patient's true pathology in a timely manner helped ensure that he would receive treatment sooner, and thus improve his quality of life.

When used appropriately, ESR testing offers the potential of cost saving benefits. In this case study, the elevated ESR results prompted further testing, which obviously did not reduce expenses. However, the ESR results did help to streamline the diagnostic process, eliminating unnecessary testing and practitioner visits that would have undoubtedly raised costs. Similar monetary benefits would also materialize in cases where normal ESR results were obtained, in that costly follow up testing would not be pursued.

In addition to lowering medical expenses, properly interpreting ESR results in conjunction with patient symptoms can also act to reduce mental anxieties associated with unknown health issues. Here, abnormal ESR results gave the practitioner reason to suspect, and justification to further investigate, a pathologic process. On the other hand, normal ESR results in similar clinical scenarios could provide the patient and practitioner reassurance that an underlying condition is not being overlooked.

Although these examples have firmly established its value, the clinical function of the ESR is easily negated if it is not used judiciously and in consideration of the patient-specific details in each situation. The current case demonstrates appropriate utilization—an ESR ordered on a symptomatic patient where pathology seemed possible. The ESR was not ordered to identify the specific diagnosis, and should not be used in that capacity because of its non-specific nature. In other words, using a 'needle in a haystack' analogy, an ESR should not be utilized to find the needle, but rather to help determine if a needle is present and/or worth pursuing. Similarly, ordering an ESR on an asymptomatic patient is counter-productive and would most likely lead to circumstances in direct opposition of the aforementioned clinical benefits.

CONCLUSION

The ESR is a simple, inexpensive laboratory test with decades of chronicled clinical use. Despite its historical importance, the ESR is often considered as inferior to more specific assays, and thus its clinical utility is often questioned. As evidenced in the discussed case study, significant merit still exists for the ESR—from eliminating unnecessary testing, to decreasing medical expenses, to providing reassurance to patient and practitioner alike. Thus the ESR, when used in the proper context of patient symptoms and history, ultimately has the power to improve patient care. In this capacity, the ESR should be regarded not only as an influential measure of the past, but also as a worthy clinical tool for current and future practitioners.

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