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REVIEW

Erythrocyte sedimentation rate – an old marker with new applications

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Abstract

Erythrocyte sedimentation rate (ESR) is an inexpensive and simple test for evaluating the inflammatory or acute response. The ESR is a useful test in clinical practice as an indicator of inflammation, infection, trauma or malignant disease. The ESR can also be an important prognostic factor in non-inflammatory conditions, such as coronary heart disease, stroke, heart failure and prostate cancer. There are several methods for measuring the ESR, but the International Committee on Standarization in Hematology Reference Procedure accepts the Westergren method developed in the early 20th century. The aim of this work is to describe and evaluate the possible application of the ESR in modern clinical practice. In conclusion, the ESR evaluation, as a cheap method, may be a good alternative to newer and more expensive methods like C-reactive protein (CRP) determination.

Key words

erythrocyte sedimentation rate, C-reactive protein, inflammation, rheumatic diseases, coronary heart disease, cancer

INTRODUCTION

Erythrocyte sedimentation rate (ESR) is an inexpensive and simple test for evaluating the inflammatory or acute response. It was discovered by the Polish physician Edmund Biernacki in 1897, but his discovery remained unknown for many years. The test was rediscovered and introduced to the scientific world in 1918 by the Swedish heamatologist and pathologist Robert Fahraeus who initially used the ESR as a pregnancy test [1]. The ESR is the most widely used laboratory measure of disease activity in clinical medicine and still remains a useful tool for monitoring inflammatory diseases, in particular, rheumatoid arthritis [1]. Normal values of ESR depends on age and gender, and present themselves as follows:

- 12-17 mm/hr for infants < 6 months;
- 15 mm/hr or less for men < 50 years old;
- 20 mm/hr or less for men > 50 years old;
- 20 mm/hr or less for women < 50 years old;
- 30 mm/hr or less for women > 50 years old [2].

ESR values in healthy volunteers increase with age, and a formula for calculating the maximal normal ESR at any age has been proposed [2]. The ESR value increases by 0.85 mm/h for each 5-year increase in age. This may be caused by elevated levels of fibrinogen or higher occult disease prevalence in the elderly [3]. But the highest normal ESR values appear to be among people aged 65-74 years [4]. The elevated ESR increases the probability of disease at any age [2]; however, physicians should remember that in many patients no cause will be found for an elevated ESR. The Internatinal Committee for Standarization in Hematology (ICSH) recommends the use of the Westergren method to measure the ESR [5]. The ESR reflects red blood cell aggregation and is the measured fall or setting of a vertical column of erythrocytes within 1 h when held vibration free, and at room temperature [3]. Blood samples can be stored for up to 24 h at 4°C. Venous blood with anticoagulant (ethylenediaminetetraacetic acid – EDTA) is diluted 4:1 with sodium citrate and placed in a 200-mm glass tube with a 2.5-mm internal diameter. At the end of 1 h, the distance from the meniscus to the top of the column of erythrocytes is recorded as the ESR in units of millimetres per hour [3]. Erythrocyte aggregation is affected by 2 major factors: red cell surface charges and frictional forces around the red cell. The erythrocytes normally have negative charges and repel each other [6]. High molecular weight proteins increase viscosity and favour rouleaux formation, and thus would raise the ESR. Fibrinogen, the most abundant acute phase reactant, has the greatest effect on the elevation of ESR in comparison to other acute phase proteins [7]. Paraproteins (positively charged molecules), when abundantly present – as in multiple myeloma or Waldenstrom macroglobulinemia – will increase the ESR levels by enhancing rouleaux formation and elevating plasma viscosity[2, 7]. For this reason, plasma viscosity measurement correlates with the ESR, but it is not as reliable as that of ESR since it is marginally affected by short-term changes in acute phase responses [2]. *In vitro* studies have shown that after isolation of erythrocytes from healthy volunteers, the ESR increased when albumin was added to a mixture of fibrinogen and immunoglobulin. However, in the same system and in hypoalbuminemic plasma, the addition of albumin decreased the ESR. Therefore, in clinical situations in which the albumin is normal, the ESR will only be affected by the level of acute phase reactants such as fibrinogen, whereas in hypoalbuminemic inflammatory states the ESR may be more elevated than if the serum albumin was normal [8]. Extremely elevated ESR (value exceeding 100 mm/hr) is strongly connected with serious underlying diseases such as collagen vascular diseases, metastatic tumours or severe infections [9]. In a study of 1,006 outpatients, the researchers found 42 cases with ESR > 100 mm/hr, and 37 with an ESR between 75-99 mm/h. There was an identifiable cause in 90%

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of the former compared with 54% of those with the more moderate rise [10].

In a study with patients of ESR > 100 mm/h infections were found to be the most frequently associated diseases (35%), while malignant diseases accounted for only 15% of the patients [11]. Other causes of increased ESR are anemia, macrocytosis, increased number of high molecular weight proteins in the blood, low hematocrit, hypercholesterolemia, nephrotic syndrome, severe liver injury, pregnancy and thyreoiditis [12]. On the other hand, conditions like hypofibrynogenemia, hypogammaglobulinemia, polycythemia, microcytosis, hemolytic anemia, hemoglobinopathies, heart failure, allergic diseases and anti-inflammatory drugs can reduce the ESR value [13].

Despite all these drawbacks, the ESR still plays an important role in the diagnosis and follow-up of rheumatoid arthritis and temporal artheritis. ESR has also been reported to be of clinical significance in sickle cell disease, osteomyelitis, stroke, coronary artery disease and prostate cancer. Therefore, the ESR is important in the diagnosis of inflammatory conditions and in the prognosis of non-inflammatory conditions [14]. The ESR should serve only as a guide and not as a screen, and only in symptomatic patients [6]. Current studies suggest that the ESR when elevated remains high until the primary inflammatory process is resolved [15].

Recently, researchers have conducted several studies which illustrate that the ESR may have more uses in clinical practice than expected. Despite its comparatively low sensitivity and specificity in monitoring disease activity, the simplicity to perform and the low cost make ESR an attractive alternative to newer methods, e.g. CRP-determination in daily clinical practice. The introduction of automated ESR instruments can improve the quality control, reduce the sample handling risk, and improve the speed of result availability [16].

Rheumatic diseases. The purpose of this section is to briefly analyze the implementation of acute phase reactants (APR) like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in rheumatic diseases. Since the theme of CRP and ESR recurs in scientific research, it is possible to enumerate the factors that have an essential impact on diagnosis, monitoring and treatment in different rheumatic diseases. The cause of rheumatic diseases is an immunological process and non-specific, chronic inflammation. According to scientific research, the inflammatory biomarkers APR should be used by physicians to monitor the activity of rheumatic diseases. This approach has many advantages. Even simple tests, such as ESR, are important for the care of patients with rheumatic disease. During the acute phase, response to a local or systemic inflammatory process, CRP and ESR rapidly increase. Analysis of inflammatory biomarkers, together with clinical and laboratory data, is used to monitor the activity of a disease [7]. Rheumatologists have distinguished a few diseases, among them, rheumatoid arthritis (RA), systemic lupus erythomatosus (SLE), ankylosis spondylitis (AS) and psoriatic arthritis (PA). The most common disease in which CRP and ESR are very sensitive indicators of disease activity is rheumatoid arthtritis (RA). This is the most common joint disease and has a prevalence of 1-2% worldwide. RA is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but in particular it attacks the synovial joints. There is a wide range of tests which are used to monitor the disease, including CRP and ESR. Both of them are used to observe disease activity and to predict how well someone is responding to treatment. ESR is not a perfect test because it is influenced by various factors, such as age, gender and anemia [13]. Therefore, CRP is a test more sensitive to changes in the disease activity than ESR. CRP reflects immediate changes and is not influenced by the same factors. The levels of CRP correlate stronger with treatment and radiographic progression than ESR. High levels of CRP in the early stage of RA are noticed in patients with a worse prognosis and the existence of progressive RA. High CRP and ESR levels are concomitant with raised levels of rheumatoid factor (RF) or anti-cyclic citrulinated peptide (anti-CCP). Finally, CRP is a direct measure of the acute-phase response, and therefore more precisely reflects RA activity. It might be more useful in clinical practice. Studies have shown that high CRP and high ESR levels are usually observed in groups of patients with the worst clinical status. What is more, the following results indicate improved clinical status, in ascending order: low ESR/ high CRP, low CRP/ high ESR, low CRP/ low ESR. The studies show that ESR can be a better choice for initial follow-up, expecially for patients with early RA. However, it should not be forgotten that the initial level of ESR does not correlate with the presence of anty-cyclic citrullinated peptide [13]. The ESR and CRP results are a part of rheumatoid disease activity scales [13]. There are a few contemporary scales available: the Disease Activity Score (DAS), Disease Activity Score 28 (DAS 28), Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI). The DAS and DAS 28 scales include ESR, the SDAI scale contains CRP, whereas the CDAI has none of the APR. The major scoring system for evaluating disease activity in patients with RA is the DAS 28 scale [17], founded on 28 tender and swollen joints, the health assessment of a patient, a visual analog scale (VAS) and ESR. A more recent modification is the DAS 28 using CRP instead of ESR. This is justified by the arguments mentioned above. The use of DAS 28 has been officially recommended by the European League Against Rheumatism (EULAR), but it is difficult to use in a daily clinical practice [17]. The SDAI and CDAI scales are simpler and more comprehensive tools. The CDAI scale, as mentioned, is the only index that does not incorporate an acute-phase response. For that reason it can be used everywhere. Taking CRP or ESR into consideration while assessing the disease activity increases the validity of these scales [18].

The second widespread disease recognized in rheumatology is Systemic Lupus Erythomatosus (SLE). Contrary to RA, SLE is a rheumatic disease in which APR does not indicate clinical activity of the disease [17]. In patients with SLE, the accumulation of CRP is frequently normal or slightly elevated, even in patients with active disease. In this disease, levels of IL6 correlate better with clinical disease activity than CRP levels. An elevated level of CRP in SLE often indicates the coexistence of another disease [13]. High CRP levels are usually linked to infection or any contagious diseases. On the other hand, slightly increased CRP levels in SLE patients may also be associated with atherosclerosis, and subsequently, with cardiovascular heart disease, stroke, and sudden heart death. In other rheumatic diseases, for instance ankylosis spondylitis (AS) and psoriatic arthritis (PA), there is no evidence of a correlation between ESR and the severity of enthesitis. It is known that 50-70% of patients with active AS present also elevated CRP levels. The scale which monitors AS activity is called The Bath Ankylosing Spondylitis Disease Activity Index

(BASDAI). This scale has been proved to correlate stronger with CRP levels than with ESR or other inflammatory factors, such as haptoglobin or beta-2-microglobulin [18]. The results of studies showing a correlation between the levels of ESR and clinical response to treatment with infliximab seem to be very interesting. However it has also been proved that the sensitivity and specificity of that factor is too low for use in clinical practice. ESR is considered to be a hallmark in giant cell artheritis (GCA), and it has been joined to the classification criteria (ESR > 50mm/h as one of 5 criteria to be used in the classification of GCA). It is usually elevated in acute untreated disease and returns to normal values after treatment. The studies showed that the value of ESR has a significant positive correlation with other parameters reflecting the acute-phase response, such as anemia, fever and weight loss [3]. ESR > 30mm/h is considered to be the main laboratory parameter to arouse suspition of GCA in patients with a compatible clinical picture. It would also help to prevent cases of GCA being missed. ESR has also been proved to be a good marker of disease activity in GCA as well as in polymialgia rheumatica [19]. Studies comparing the clinical spectrum of disease, laboratory data or outcome in 2 groups (patients with ESR < 50mm/h – group A and patients with ESR > 50mm/h – group B) did not prove any significant differences. ESR levels have a positive correlation with such variables as anemia, weight loss, elevated liver enzymes and fever. The correlation between low ESR and delay of diagnosis of GCA has not been observed. The measurement of CRP and ESR in giant cell artheritis can be a useful marker of a clinical response to prednisone. Patients with lower ESR respond to lower doses of prednisone and present earlier remission. Both ESR and CRP present also excellent negative predictive values [19].

The aim of this section was to indicate the usage of APR in diagnosis, monitoring and treatment in various rheumatic diseases. Although the implementation of APR may be at variance in different diseases, it does have positive sides. Despite the advantages of CRP and ESR tests, they are frequently underestimated by physicians in everyday clinical practice. The lack of APR leads to ignoring inflammatory indices in rheumatic disease. Furthermore, the treatment of the patients is not consistent: consequently, patients are deprived of suitable therapeutic decisions and possible benefits of intensifying therapy.

Coronary heart disease. Accelerated erythrocyte aggregation can be explained by the action of several large, asymmetrical, plasma proteins which inhibit the negative electrical forces that normally keep the erythrocytes apart. An increased level of such proteines as fibrinogen, immunoglobulins, lipoproteins, and alpha-2-macroglobulin is considered to be responsible for this effect. Proteins which facilitate thrombocyte aggregation and cellular adhesion and migration might conceivably also alter erythrocyte membranes and increase their propensity to aggregate [3]. The correlation between the substances liberated from atheromatous tissue and the rate of erythrocytes aggregation is largely unknown and should be studied further. Such factors as smoking, obesity, elevated blood pressure, elevated cholesterol and triglyceride levels, diabetes, or infection are known to increase the fibrinogen level [8]. On the other hand, alcohol consumption and hepatitis B surface antygen are expected to give an opposite effect. Notably, ESR retains its strong predictive power, even after adjustment of all those factors, and the correlation between fibrinogen levels and ESR could not be assessed in a single report [5]. Chronic inflammation in the wall of the vessel is connected with the numbers of inflammatory cells involved. It can also be caused by bacterial or viral infections or autoimmune diseases. Both humoral and cell mediated immune mechanisms are involved in atherogenesis. High cellularity of the plaque markedly increases the risk of rupture and development of acute atherothrombotic complications. Humoral responses connected with highly cellular atheromas contribute to the increased ESR [2]. Autopsy studies have shown that at the time of coronary heart disease (CHD), atherosclerosy is a generalized disease, involving usually more than 50% of total surface of coronary vessels. Increased ESR may be correlated with the intensity of that process and also it could be used as a marker of advanced coronary heart disease with high risk of arterial thrombosis [4]. Reference values of ESR among healthy men have not been established.

Values under 10mm/h are recommended for men below 50 years of age and <14 for men over 60 [2]. Scientists from Oslo University in Norway considered the erythrocyte sedimentation rate as an important marker of arterosclerosis, and a strong predictor of mortality in coronary heart disease. To support their theory, they conducted a survey in 1972-1975 [11] among participants recruited from 5 Norwegian companies. All of them were apparently healthy men between the ages of 40-60, which meant the absence of recognized heart diseases, hypertension, cancer, diabetes mellitus, or any other serious diseases. All the participants were expected to conduct a symptom limited exercise ECG, although the positive result was not among the exclusion criteria. Eight years later, the men who remained healthy according to the baseline inclusion criteria, were used for assessing the possible significance of alternations in the rate of erythrocite sedimentation. Participants were divided into 5 groups, according to intervals of ESR: 0-4, 5-9, 10-14, 15-29 and >30mm/h. Significant correlations were found for age, heamoglobin level, smoking status, total cholesterol level, and systolic blood pressure. Weaker but significant correlations were found for triglycerides, fasting blood glucose and physical activity level. Subjects with low ESR had more favourable values for a number of coronary heart disease risk factors than the men with ESR in the higher ranges. Also, the correlation between increasing ESR values and mortality of coronary heart disease and cardiovascular disease was proved [11]. Proportional hazard analyses show that in the Survey 1, ESR was a strong predictor of coronary heart disease mortality after 23 years, less so for cardiovascular disease mortality, and non-significant for cancer and non-cardiovascular disease mortality. The predictive power of Survey 1 ESR remained virtually unchanged during the whole observation period. An increase of coronary heart disease mortality with ESR > 15, both among men with angina pectoris and those with silent ischemia, has been proved, although coronary heart disease among patients with angina was highest in all ESR groups. Furthermore, the percentage of participants developing non-fatal myocardial infarctions in the baseline ESR group of 15-29 mm /h was similar to the event rate among those with normal baseline sedimentation rates. Only the group whose ESR was higher or equal of 30 mm/h had an elevated frequency of myocardial infarction, but the numbers of patients in this subgroup were extremely small. It would seem that the value

of ESR as a factor of subsequent development of non-fatal myocardial infarction has a very poor predictive accuracy [12]. Patients with elevated plasma C-reactive protein and low albumin have an increased risk of coronary arteries disease of about 50%. In the group of patients with elevated ESR (>14 mm/h), only 27.9% developed one or more myocardial infarctions [9]. ESR emerged as a strong short- and long-term predictor of coronary heart disease mortality, and carries the same relative prognostic information, both among healthy men, men with a positive exercise ECG tests results, and men with angina pectoris [2]. Moreover, with increasing ESR, there was a much steeper gradient in the percentages of men dying from coronary heart disease without prior myocardial infarction, than in the percentage of men who had had one or more myocardial infarction [1]. Thus, the predictional usefulness of ESR for men and women over the age of 60 (where coronary heart disease is more prevalent) has not yet been proved [11].

A longitudinal population study from Goetteborg, Sweden, of ESR as a predictional factor of subsequent coronary arterial disease in a population of women did not prove its value. More studies are needed to explain why an increased level of C-reactive protein corellates with risk of subsequent development of myocardial ischemia in the population of women, while the ESR does not [12]. Analyses by Danesh, Collins, Peto and Lowe [20] showed a significant correlation between ESR and subsequent coronary arterial disease, in whch 1,703 fatal and non-fatal coronary heart disease cases were analysed. Comparing ESRs in individuals in the top third with those in the bottom third at baseline, revealed a risk ratio of 1:33. Similar analysis of the relationship of haematocrit, involving over 8,000 patients with coronary heart disease, showed a result of 1:16, and for plasma viscosity (in several different analyses involving 1,278 cases), the result was 1:57 [4]. It has been proved that reological properties of blood correlate with the subsequent development of coronary heart disease in a population of middle-aged patients. However, the authors' claim that the value of measuring ESR for this purpose has not yet been established [3]. However, the measure of ESR has relatively poor sensitivity as a marker to detect a first myocardial infarction, there should be a reason above and beyond its simplicity of performance and low costs to justify its use in daily clinical practice [13].

In summarising our considerations, it should be borne in mind that most coronary heart disease decendents have normal or only slightly elevated ESR. Although elevated ESR can be used as an indicator of the malignant, aggressive form of CHD, in the group of high risk patients only 10% had ESR>15mm/h. The risk associated with ESR> 15mm/h is comparable to total cholesterol level of > 8mmol/l. However, generalized atherosclerosis potentially results in vulnerable plaques, not only in the coronary arteries, but also in the aorta and carotid arteries [9]. There is insufficient evidence to add ESR to the list of markers – there exists only a little data for women and restricted data for men. Some authors claim that ESR failed to predict subsequent non-fatal myocardial infarctions in men and it has limited value, even if it does predict CHD mortality.

Chronic heart failure. In recent years, there has been a considerable increase in interest in the correlation between inflammatory markers, such as ESR, and cardiovascular diseases. Inflammation has emerged as a crucial part of the artheriosclerosis process. It can be indicated in vessels as a response to different factors, such as low-density-lipoprotein cholesterol, injury or infections. Most common risk factors of cardiovascular diseases have also been associated with low-grade chronic inflammation. Observations indicate that inflammation may be an important factor that occurs early in the process leading to the heart failure [3]. Proinflammatory cytokines, such as TNF-alpha, can depress myocardial contractility and affect left ventricular remodeling through local induction of matrix metalloproteinases. Inflammation can also induce endothelial dysfunction in small vessels, and thus result in an impaired coronary flow and impaired left ventricular function [7].

ESR has been analyzed as a possible predictor in heart failure (HF) during a median follow-up time of 30 years in a sample of middle-aged men free from HF, previous myocardial infarction, and valvular disease at baseline. The incidence rate of HF during the follow-up period was 4.8/1,000 person-years at risk. ESR has been proved to be significantly associated with HF incidance, and the highest hazard ratio was observed in the highest quartile of ESR, compared with the reference level. ESR measurement as a diagnostic test for future HF has been assessed as quite a good tool (sensitivity 48%, specificity 57%, positive predictive value 13%, negative predictive value 89%). The predictive value of ESR in a subsample free from corticosteroids and anty-inflammatory analgesics was essentially the same as in other groups [6]. It has also been proved that the diagnostic capacity of ESR as a test for incident HF, in terms of sensitivity and specificity, was comparable with that of hypertension. Recent studies have reported that in patients with manifest HF, a high ESR is associated with a more severe stage of HF, and a worse prognosis [3]. An increased ESR is a strong predictor of impaired survival in patients with CHF, independent of established risk factors such as New York Heart Association (NYHA) class, LVEF or peak VO2. On the other hand, the studies by Haber showed that high ESR levels indicated better survival in 242 patients with CHF in III and IV NYHA class (treated with digitalis and diuretics). These results are in agreement with the findings of Paul Wood in 1936 [21], when he reported on 22 patients with heart failure. He discovered that ESR decreased when heart failure worsened, and rose again when the condition improved. There is no reason to doubt the results of previous studies, even if the results are diametrically opposed. The most important difference seems to be the treatment with angiotensin-converting enzyme (ACE) inhibitors. That fundamental change can be explained in the following way: patients with high ESR may be those who were able to respond adequately to metabolic and immunological abnormalities; therefore those patients had a more favourable outcome [6]. Patients with low ESR were compromised in their responsiveness and died earlier. When the new treatment was started, most measures of heart failure improved and the ESR was found to increase proportionally to the severity of heart failure. ACE has been found to be able to suppress lipopolisaccharide-inducted production of TNF- alpha. Other different treatments being used in chronic heart failure (beta-adrenergic blocking treatment) may have similar metabolic effects. There was no correlation between the dose of ACE inhibitors and the levels of ESR [7].

Chronic obstructive pulmonary disease. ESR may be considered as a less expensive alternative to C-reactive

protein marker of systemic inflammation in chronic obstructive pulmonary disease. It increases in response to rising serum levels of acute phase proteins, fibrinogen and immunoglobulines, as well as in response to anemia. This may seem to be an advantage in the assessment of patients with Chronic Obstructive Pulmonary Disease (COPD) as that disease is mainly connected with anemia and hyperfibrinogenemia. ESR should be considered as a potential index of COPD severity, especially when considering COPD as a systemic and not only respiratory disease. The prospective of using ESR as a marker should be strenghted by well-standarized and reproducible procedures of measurement. It is also worthwhile mentioning that such an almost cost-free procedure is well suited for low-income countries, where the prevalence of COPD is dramatically increasing [11]. Scientists from several universities in Italy worked together to discover whether ESR qualifies as a low-cost alternative to CRP as a marker of COPD severity. 223 consecutive outpatients aged 65 or over, with stabile COPD were grouped according to normal or increased values of ESR and CRP [16]. Patients with diagnosis of cancer were excluded as selected effects of cancer might simulate effects of COPD. ESR was measured using a modified Westergren method. The following variables were taken into consideration, according to the levels of ESR: age, gender, PaO2, FEV1 (forced expiratory volume in the first second), 6-m-WT (six-minute walk test), body mass index, waist circumference, cardiovascular diseases, diabetes, renal failure, hypoalbuminemia and anemia. The correlations between ESR, CRP and selected variables of interest were assessed by Spearman's test and multivariate linear regression analysis. Results of the tests showed that CRP is weakly and inversely connected with the FEV1, but there was no such correlation for ESR [2]. CRP and ESR shared the same inverse correlation with serum albumin, but only ESR was inversely correlated with heamoglobin level. There was no significant relationship between ESR and COPD severity expressed by GOLD stages. Patients with high ESR values had slightly reduced values of FEV1, and were often affected by hipoalbuminemia and anemia (low albumin likely qualifies as an indicator of increased circulating acute phase reactants) [3]. The highest prevalence of renal failure was in the group with low CRP and high ESR levels. In the group with high CRP and ESR levels there was an evident trend towards lower PaO2 values. The study showed that ESR and CRP are not interchangable indexes of inflammation, but are concordant in the stable COPD. The authors proved that CRP may reflect a greater sensitivity to chronic lung inflammation as ESR is unrelated to bronchial obstruction.

It is worth mentioning that ESR may be increased despite normal CRP in anemic patients [3]. The highest prevalence of hypoalbuminemia, anemia, and the lowest FEV1% was observed in the group with high values of CRP and ESR [16]. It was also observed that the lack of decline of ESR correlates with high risk of re-infection and worsening health status [5].

To summarise, the authors admit that ESR might be more useful as a marker of COPD exacerbations than as a marker of disease severity. However, CRP seems to be more sensitive in respiratory infections or exacerbated COPD. In conclusion, neither ESR nor CRP qualifies as a potential marker of COPD-related systemic inflammation.There is also no reason to consider ESR as a low-cost alternative to CRP [11].

To assess the clinical value of laboratory parameters, including ESR, patients with an unfavourable clinical outcome were compared to patients with a favourable outcome. It was proved that ESR, as well as CRP and orosomucoid, correlate with disease activity [22]. The results showed poor diagnostic accuracy of inflammatory variables. After calculation of specificity and sensitivity with regard to laboratory tests, the most favourable results were found for CRP, leukocyte and granulocyte count, and only to a lesser extent for ESR. However, none of the laboratory parameters was able to distinguish a group of patients who were likely to have a poor outcome from a group of patients who were likely to achieve remission [22]. The authors admit that both inflammatory and coagulation variables did not seem to be effective in predicting the course of disease. In the studies by Bodelier *et al.* [23], they investigated a correlation between clinical activity index and the biochemical markers, such as ESR in IBD. A weak but significant correlation between ESR and Harvey Bradshav clinical activity index (HB) was shown. ESR correlated significantly with calprotectin in UC but not in patients with Crohn's disease (CD). However, none of biochemical markers is specific and sensitive enough to be useful in non-invasive assessment of disease activity [22].

Childhood bone and joint infections. 265 children aged between 3 months and 15 years with culture positive osteoarticular infections were monitored with a predetermined series of measurements of different inflammatory markers, including ESR. ESR exceeded 20mm/h in 94% of the patients, and it normalized in 24 days. CRP seemed to give a slightly better sensitivity in diagnostics than ESR, but the best sensitivity was obtained with the combined use of ESR and CRP (combining both markers gives 98% sensitivity) [24]. No correlation was observed between ESR and CRP elevated levels and the surgical procedure undergone. However, it has been recommended that ESR should be measured only on arrival, because in some cases, the first CRP value was less than 20mg/dl. In that case, the measurement of ESR can provide some additional information in diagnostics. ESR still seems to be the main yardstick in monitoring the illness. Unfortunately it normalizes so slowly that active infection is likely to have resolved earlier than the ESR levels normalize [24].What is more, CRP seems to be faster than ESR and the White Blood Count (WBC) in predicting the effectiveness of therapy. The most significant clinical information is that we can rule out bacterial osteoarticular infection if CRP and ESR remain normal for 3 days [24].

Neoplasma. The ESR tends to increase in patients with cancer, particularly as the disease progresses. It has been reported that the ESR values are elevated in patients with metastatic breast cancer [25]. Cheung *et al.* [26] in their study emphasized the role of blood markers in the diagnosis and monitoring of metastatic breast cancer. They have shown that a combination of different markers is better than any single marker in metastatic breast cancer. The most common combination of markers is CA 15.3 and CEA, which gives a sensitivity of over 80% for detecting metastatic disease [27]. When these 2 markers are combined with ESR, the sensitivity can reach above 90% [24]. Blood tumour marker measurements are more objective than the inetrpretation of imaging in metastatic breast cancer. A combination of CA15.3, CEA and ESR enables biochemical assessment in

practically 100% of patients [28]. Biochemical evaluation provides the only validated method for assessing the response to systemic therapy for disease unassessable by the Union for International Cancer Control (UICC) criteria. In the Guidlines for the Management of Metastatic Bone Disease in Breast Cancer, blood markers (CA15.3, CEA and ESR) measurement is also recommended as a valuable tool in monitoring therapy [29]. Biochemical evaluation may result in more than 50% cost-savings in comparison to conventional assessment by clinical/radiological criteria which often involve expensive imaging techniques [30]. In a prospective study of 300 patients with prostate cancer, the ESR 37 mm/hr was connected with a higher prevalence of disease progression and death. But these findings require further investigation [2]. An increased ESR is also helpful in suspecting multiple myeloma and other paraproteins, but it is not included in the diagnostic criteria for these conditions [31].

The ESR is one of several parameters that allow distinguishing benign monoclonal gammapathy from malignant multiple myeloma [32]. Increased levels of inflammatory markers such as ESR or CRP (particularly very high values) may indicate a neoplastic disease, and phycisians should search for tumour when other causes have been excluded.

CONCLUSIONS

The ESR is an old but still widely used test, although no guidelines have been established for its use. It has an important role in temporal arteritis, polymyalgia rheumatica, rheumatoid arthritis and myeloma. It may have new potential applications in some conditions, such as coronary heart disease, prostate cancer and osteomyelitis. Clinicians should remember that this test is only one parameter which can be useful in the diagnosis and follow-up of certain inflammatory conditions, and it can also be a prognostic tool in non-inflammatory diseases.

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