Clinical Significance of Extreme Elevation of the Erythrocyte Sedimentation Rate

Ruth-Marie E. Fincher, MD, Malcolm I. Page, MD

• **Charts of 1006 consecutive outpatients were reviewed to ascertain the cause of extreme elevation of the erythrocyte sedimentation rate (ESR) (≥100 mm/h) and the sensitivity of marked ESR elevation in patients with disorders commonly reported to cause ESR elevation. Prevalence of ESRs of 100 mm/h or more was 4.2%. Infection was the most common cause (33%), with malignant neoplasms and renal disease each responsible for 17% and inflammatory disorders for 14%. Only 1% of all other patients had ESRs of 100 mm/h or more. An ESR of 100 mm/h or more had low sensitivity: 36% among patients with infection, 25% among those with malignant neoplasms, and 21% among patients with noninfectious inflammatory disorders. Specificity was high, both for individual disease categories (96% for malignant neoplasms and 97% for infection) and as a "sickness" index (>99%). The positive predictive value for an identifiable cause of marked ESR elevation was 90%.**

(*Arch Intern Med* 1986;146:1581-1583)

The erythrocyte sedimentation rate (ESR) is a commonly determined, inexpensive laboratory measure often considered to be a nonspecific indicator of underlying systemic disease.[1-5] In 1967, Zacharski and Kyle[1] reported a 58% frequency of malignant neoplasms in patients with a Westergren ESR greater than or equal to 100 mm/h. More recently, inflammatory disease, especially infection, has been reported to be the most common cause of marked elevation of the ESR.[2-7]

Previous studies[1-5,7] have documented the causes of extreme ESR elevation in consecutive patients in whom the ESR was greater than 100 mm/h. However, none of these studies reported the prevalence of ESRs greater than 100 mm/h in a population of patients with a given disease. The current study was undertaken to (1) ascertain the cause of extreme elevation of the ESR (defined as ≥100 mm/h) in an outpatient population, (2) assess the diagnostic significance of moderate elevation of the ESR (defined as 75 to 99 mm/h), (3) determine the sensitivity of extreme ESR elevation for disorders frequently reported to cause ESR elevation, and (4) assess the specificity of marked ESR elevation as a "sickness index."

Accepted for publication Dec 4, 1985.

From the Section of General Internal Medicine, Department of Medicine, Medical College of Georgia, Augusta.

Reprint requests to Department of Medicine, BD-141, Medical College of Georgia, Augusta, GA 30912 (Dr Fincher).

PATIENTS AND METHODS

During the two-year period from Jan 1, 1982, to Dec 31, 1983, a total of 1080 outpatients were evaluated in the ambulatory Medical Consult Clinic at the Medical College of Georgia Hospital, Augusta, a state-supported, tertiary referral hospital. All patients gave a complete history and underwent physical examination, complete blood cell count, determination of ESR, 18-factor automated chemical analysis, rapid plasma reagent determination, urinalysis, chest roentgenogram, and electrocardiogram. The patient population was unselected and was composed primarily of patients referred because of financial constraints. No patient was referred for evaluation of elevated ESR. The ESR was determined by the Westergren method.

The study group was composed of 1006 patients, selected on the basis of availability of charts and completeness of laboratory data. Between September and December 1984, all charts were reviewed and the pertinent clinical and laboratory data, as well as diagnoses formulated as a result of the clinic consultation, recorded systematically on a flow sheet. To evaluate the diagnostic significance of an elevated ESR, the most likely cause of each ESR greater than or equal to 100 mm/h and for each ESR between 75 and 99 mm/h was determined by one of us. The extent of the diagnostic evaluations varied; each patient was evaluated as extensively as the Consult Clinic faculty physician believed was indicated. The level of elevation of ESR did not appear to influence the workup in any patient. Because the patients for the study were from an outpatient consultation clinic, long-term follow-up was not possible in the majority of patients.

RESULTS

Of the 1006 patients in the study group, 750 (75%) were female and 557 (56%) were black. The mean age was 43.7 years (range, 13 to 89 years). There were 42 patients with ESRs of 100 mm/h or more (a prevalence of 4.2 per 100 patients) and 37 patients with an ESR between 75 and 99 mm/h (a prevalence of 3.7 per 100 patients). In the black population, 33 patients (6%) had extreme elevation of the ESR, whereas in the white population only nine patients (2%) had elevation of the ESR to 100 mm/h or more (Table 1). This difference between black and white patients was significant ($P = .005$). While there was no significant difference between black and white male patients (6% vs 3.9%; $P = .1$), the difference between black and white female patients (6% vs 1.6%) was highly significant ($P < .005$). Overall, there was no difference in the frequency of markedly elevated ESR among male and female patients (5.5% vs 3.7%). Of the 42 patients with extreme ESR elevation, 38 (90%) had a single identifiable cause, compared with 20

Downloaded from jamanetwork.com by Harvard University user on 10/27/2026

Table 1.—Race and Sex Distribution of 1006 Patients With Elevated ESR*

	Black	White	Total
Female			
No.	378	372	**750**
No. (%) with ESR ≥100 mm/h	22 (6)†	6 (1.6)	**28** (3.7)
Male			
No.	179	77	**256**
No. (%) with ESR ≥100 mm/h	11 (6)	3 (3.9)	**14** (5.5)
Total			
No.	**557**	**449**	**1006**
No. (%) with ESR ≥100 mm/h	**33** (6)‡	**9** (2)	**42** (4.2)

*ESR indicates erythrocyte sedimentation rate.
†$P<.005$ vs white female patients (χ^2 test).
‡$P<.005$ vs white patients.

(54%) of the 37 patients with moderate ESR elevation (Table 2).

Cause of ESR Elevation

Infection was the most common cause of extreme ESR elevation, occurring in 14 (33.3%) of the 42 patients. In these 14 patients, pulmonary infections were most common, identified in six patients (bacterial pneumonia in three, lung abscess in two, and tuberculosis in one). Three patients had urinary tract infections, two had syphilis, and one each had liver abscess, acquired immunodeficiency syndrome with fever, and gangrenous foot. Among the 37 patients with moderate ESR elevation, infection was present in six patients (16%). Two patients had infectious diarrhea, two had urinary tract infections, and two had pulmonary infections (tuberculosis in one and bronchiectasis in one).

Renal disease was present in seven patients (16.7%) of the 42 with markedly elevated ESR. All seven patients with renal disease had chronic renal insufficiency (creatinine level, >2 mg/dL [>176.8 μmol/L]), secondary to diabetes and/or hypertension in six and due to chronic pyelonephritis in one. Four (11%) of the 37 patients with moderately elevated ESR had renal disease, chronic renal insufficiency in two and proteinuria with normal renal function in two.

Of the seven patients with malignant disease and ESRs of 100 mm/h or more, six had solid tumors, all of whom had evidence of metastatic disease. Two of these had primary lung malignant neoplasms, two had metastatic disease with unknown primary, and one each had ovarian and prostate carcinoma. Of the four patients with malignant neoplasms and ESRs of 75 to 99 mm/h, one had Waldenström's macroglobulinemia and three had solid tumors. Two patients had metastatic lung cancer and one had Kaposi's sarcoma.

Inflammatory conditions, excluding infection, were present in six (14.3%) of the 42 patients with extreme ESR elevation. Four patients had collagen vascular disorders and one each had pancreatitis and chronic lead intoxication with saturnine gout. Six (16%) of 37 patients with moderate ESR elevation had various inflammatory disorders. Two patients had arthralgias and one each had rheumatoid arthritis, nonspecific vasculitis, dermatitis, and alcoholic hepatitis.

Four patients (9.5%) were believed to have miscellaneous causes of extreme ESR elevation. One patient had each of the following: newly diagnosed Graves' disease, non–insulin-dependent diabetes mellitus with neuropathy, hypergammaglobulinemia, and cirrhosis of the liver. The remaining four patients had ESRs of 100 mm/h or more without a detectable cause (Table 2). Among the 37 patients with moderate ESR elevation, 17 (46%) had no identifiable cause.

Table 2.—Cause of Erythrocyte Sedimentation Rate (ESR) Elevation Among 79 Patients

	No. (%) of Patients	
Disorder	ESR, ≥100 mm/h	ESR, 75-99 mm/h
Infection	14 (33)	6 (16)
Renal disease	7 (17)	4 (11)
Malignant neoplasm	7 (17)	4 (11)
Inflammatory disease	6 (14)	6 (16)
Miscellaneous	4 (9.5)	0 (0)
Unknown	4 (9.5)	17 (46)
Total	**42 (100)**	**37 (100)**

Table 3.—Sensitivity of Markedly Elevated ESR*

		ESR, ≥100 mm/h		ESR, >75 mm/h	
Disorder	No. of Patients	No.	Sensitivity, %	No.	Sensitivity, %
Commonly associated with ESR elevation					
Infection	39	14	36	20	51
Malignant neoplasm	28	7	25	11	39
Renal disease	29	7	24	11	38
Inflammatory disease	29	6	21	12	42
Other	881	8	1	25	3

*ESR indicates erythrocyte sedimentation rate.

Sensitivity and Specificity of ESR Elevation

The sensitivity of an elevated ESR was low in all categories of patients, ranging from 21% to 51% (Table 3). Of the 1006 patients, 39 had infections, 19 (49%) of whom had ESRs of less than 75 mm/h. Of these 19 patients with infection and ESRs of less than 75 mm/h, ten had urinary tract infections, four had tuberculosis (pulmonary in two and peritonitis in two), and one each had syphilis, gonococcal urethritis, hepatitis, perirectal abscess, and soft-tissue infection. An ESR of 100 mm/h or more had a low sensitivity of 36% (14/39) and a high specificity of 97% (939/967) for infection.

Among the 29 patients with renal disease, 18 (62%) had ESRs of less than 75 mm/h. An ESR of 100 mm/h or more had a sensitivity of 24% (7/29) for renal insufficiency, while the specificity was 96% (942/977).

Sixty-one percent (17/28) of patients with malignant neoplasms had ESRs of less than 75 mm/h. Of the 17 patients with malignant neoplasms and ESRs of less than 75 mm/h, 14 had solid tumors and one each had chronic lymphocytic leukemia, hairy cell leukemia, and multiple myeloma. Of the solid tumors, three were primary lung malignant neoplasms, two were metastatic disease with unknown primary, and two each were gastric and prostate carcinoma. In addition, one patient had each of the following: carcinoma of the colon, carcinoma of the rectum, lymphoma, hepatoma, and melanoma. Of 14 patients with solid tumors and ESRs of less than 75 mm/h, six (43%) had metastatic disease compared with all six patients with solid tumors and ESRs of 100 mm/h or more. Sensitivity of an ESR of 100 mm/h or more, therefore, was 25% (7/28) for malignant neoplasm, and the specificity, 96% (943/978).

Among the 29 patients with noninfectious inflammatory processes, 17 had ESRs of less than 75 mm/h. Seven had

Downloaded from jamanetwork.com by Harvard University user on 10/27/2026

reflux esophagitis or gastritis, four had sarcoid, two each had dermatitis and Sjögren's syndrome, and one each had ulcerative colitis and autoimmune thyroiditis. Sensitivity of an ESR of 100 mm/h or more was 21% (6/29) for noninfectious inflammatory processes (Table 3), while the specificity was 96% (941/977).

While the sensitivity of an ESR of 100 mm/h or more was low for all diagnostic categories, the specificity was high, both for individual diagnostic groups and for the collective group of considered diagnoses. When used in this manner as a sickness index, the specificity of extreme ESR elevation was more than 99% (877/881).

COMMENT

The most common cause of marked ESR elevation was infection, occurring in 33% (14/42) of our patients. This is greater than the 8% reported by Zacharski and Kyle[1] from the Mayo Clinic (Rochester, Minn) but comparable with the 34% reported by Hart et al[3] from an inpatient population in Toronto and the 35% and 44%, respectively, reported by Wyler[5] from an inpatient population at the Massachusetts General Hospital (Boston) and Cheah and Ransome[4] from Singapore. While these differences are interesting, they may merely reflect differences in the patient populations seeking care at the various institutions. In this population, the sensitivity for infection of an ESR of 100 mm/h or more was 36% and the specificity, 97% (939/967). While the specificity for infection was high, the positive predictive value was low (33% [14/42]) due to the low prevalence of infection in the population (39/1006).

Renal disease accounted for ESR elevation greater than or equal to 100 mm/h in 17% (7/42) of patients in this series, higher than the 1% to 5% reported previously.[3-5] For the presence of renal disease, the specificity of an ESR of 100 mm/h or more was 96% (942/977), but positive predictive value, only 17% (7/42) due to the low prevalence of renal disease.

In contrast to the 58% frequency of malignant neoplasms reported by Zacharski and Kyle,[1] only 17% of patients in this study had a malignant neoplasm as the cause of the extremely elevated ESR. This result is in concert with other studies in which the frequency of malignant neoplasm varied from 12% to 23%.[2-5] Therefore, the incidental finding of an ESR of 100 mm/h or more should not initiate an exhaustive search for an occult malignant neoplasm. As in previous studies, marked ESR elevation due to malignant neoplasm was uniformly (six of six patients) associated with metastatic disease in this group. However, in patients with solid tumors who had ESRs of less than 75 mm/h, only six (43%) of 14 had metastatic disease. Sixty-one percent of patients with malignant neoplasms had ESRs of less than 75 mm/h. While the specificity for malignant neoplasm of an ESR of 100 mm/h or more was high (96% [943/978]), the positive predictive value was low (17% [7/42]) due to the low prevalence (28/1006).

The prevalence of an ESR of 100 mm/h or more was 4.2 per 100 in this population, slightly higher than the one or two per 100 previously reported.[1,2,7] While the sensitivity of an ESR of 100 mm/h or more was low for all disease categories considered, the specificity was high both for individual disorders and for the collective group of disorders commonly associated with marked ESR elevation. The positive predictive value was low for any given disease due to the low prevalence of any one given diagnostic category in the population studied. However, when all patients with infection, malignant neoplasms, renal disease, or inflammatory disorders were collectively considered, the specificity of an ESR of 100 mm/h or more was greater than 99% (877/881) and the positive predictive value was high (90% [38/42]). Therefore, when extreme ESR elevation was used as a sickness index, both the specificity and positive predictive value exceeded 90%.

The prevalence of moderate ESR elevation was 3.7 per 100 in this population. As a sickness index, ESRs of 75 to 99 mm/h had low sensitivity (15% [6/36]) and high specificity (98% [952/969]) but a positive predictive value of only 54% (20/37).

These findings are consistent with those of Bedell and Bush,[8] who found that the spectrum of specific diseases that may cause marked ESR elevation is so diverse that the ESR is not useful as a diagnostic test, but it is useful as a sickness index. In this study, when ESR was used as a sickness index, the specificity of an ESR of 100 mm/h or more was greater than 99% (877/881) and the positive predictive value, 90%. Only 10% of patients (4/42) with extreme ESR elevation had no identifiable cause (ie, false-positive). However, among the 37 patients with moderate ESR elevation, only 20 had an identifiable cause. The positive predictive value for ESRs of 75 to 99 mm/h was only 54% (20/37) and was not a useful predictor of sickness.

We wish to thank Joseph Lunn, MD, and Anne Mattas, MD, for critical review of the manuscript, Alma Bussey and Charlotte Betters for manuscript preparation, and Cindy Bishop for chart retrieval.

References

1. Zacharski LR, Kyle RA: Significance of extreme elevation of erythrocyte sedimentation rate. *JAMA* 1967;202:116-118.
2. Payne RW: Causes of the grossly elevated erythrocyte sedimentation rate. *Practitioner* 1968;200:415-417.
3. Hart GD, Soots M, Sullivan J: Significance of extreme elevation of erythrocyte sedimentation rate. *Appl Ther* 1970;12:12-13.
4. Cheah JS, Ransome GA: Significance of very high erythrocyte sedimentation rates (100 mm or above in one hour) in 360 cases in Singapore. *J Trop Med Hyg* 1971;74:28-30.
5. Wyler DJ: Diagnostic implications of markedly elevated erythrocyte sedimentation rate: A reevaluation. *South Med J* 1977;70:1428-1430.
6. Ford MJ, Innes JA, Parrish FM, et al: Significance of gross elevations of the erythrocyte sedimentation rate in a general medical unit. *Eur J Clin Invest* 1979;9:191-194.
7. Abengowe CV: Clinical importance of grossly increased erythrocyte sedimentation rate. *Can Med Assoc J* 1975;113:929-930.
8. Bedell SE, Bush BT: Erythrocyte sedimentation rate: From folklore to facts. *Am J Med* 1985;78:1001-1009.

Downloaded from jamanetwork.com by Harvard University user on 10/27/2026