Research Article

Extremely elevated erythrocyte sedimentation rate: patient diagnoses at a tertiary Indian hospitalChristol Blanch Moras¹, Ashima Nagesh Amin², Reshma Gopal Kini³^{1,2}Assistant Professor, ³Associate Professor, Department of Pathology, Father Muller Medical College Mangalore, Karnataka, India

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ABSTRACT

Introduction and Aim: Extremely elevated Erythrocyte Sedimentation Rate (EEESR) is the term commonly used for elevation of ESR more than or equal to 100mm in the first hour. To the best of our knowledge, this is the first study in Indian population. Aim was to study the common etiologies of EEESR in Indian patients at a tertiary hospital.

Materials and Methods: A retrospective, cross-sectional and descriptive study was carried out and included all patients 18 years of age and above, and who had a raised ESR of 100 mm and above at the end of 1st hour at least one time between January 2018 to December 2018 and tested at our institute. The patient's demographic details, ESR values and diagnoses were retrieved from electronic records and were divided into 7 categories like infections, malignancy, renal diseases, autoimmune diseases, mixed diagnoses, miscellaneous and unknown.

Results: During the study period, 607 patients had EEESR. There were 335 males and 272 females. The mean age was 55 years. Within the broad categories of diseases, infection was the most common cause (52%) followed in descending order by renal diseases (12.4%), malignancy (9.6%), miscellaneous (8.4%), mixed diagnoses (7.6%), autoimmune diseases (7%) and unknown (3%). In the infection category, pneumonia was the commonest.

Conclusion: This study on frequency of common etiologies of EEESR is the first study in Indian population. Our study reaffirms findings that most patients have an underlying cause for EEESR. The commonest etiology in Indian patients is infection with pneumonia being the frequent cause.

Keywords: Infection; pneumonia; renal diseases; malignancy

INTRODUCTION

ESR (Erythrocyte sedimentation rate) is an inexpensive and a simple test most widely used in clinical practice. It measures the rate at which the red blood cells sediment in a period of time and is expressed in terms of mm. Being a surrogate marker of acute phase reaction, it has been proposed by some authors to use as sickness index (1,2). The test is best used as a tool to follow the clinical course in diseases like Lymphomas, Rheumatoid Arthritis, Temporal arteritis and Polymyalgia Rheumatica (3).

Extremely elevated ESR (EEESR) is the term commonly used for elevation of ESR more than or equal to 100mm in the first hour. EEESR has numerous etiologies and is commonly associated with an underlying disease posing a diagnostic challenge to the treating clinician. EEESR is found in several diseases including malignancies, infection and collagen vascular diseases (4, 5). Currently, there is no data on the frequency of diseases with EEESR in Indian population. This study was carried out to address the frequency of common etiologies of EEESR in a south Indian tertiary hospital.

MATERIALS AND METHODS

A retrospective, cross-sectional and descriptive study was carried out and included all patients 18 years of

age and above, and who had a raised ESR of 100 mm and above at the end of 1st hour at least one time between January 2018 to December 2018 and tested at our institute. The study was approved by the ethical committee. The ESR at this hospital is carried out on whole blood samples obtained through standard venous veni-puncture techniques in black top vacutainer containing 3.8% sodium citrate anticoagulant (1.6 ml blood in 0.4ml anticoagulant). The analysis is done manually by Westergren method using Westergren pipette. Results are expressed as the fall in RBCs in mm at the end of first hour.

Inclusion criteria were all patients of 18 years of age and above, and who had a raised ESR of 100 mm and above at the end of 1st hour at least one time.

The patients' demographic details namely age, sex along with clinical diagnosis and ESR value were retrieved from electronic medical records. As in previous studies, the patients were divided into 7 categories like infections, malignancy, renal diseases, autoimmune diseases, mixed diagnoses, miscellaneous and unknown (6-8).

Those patients who had more than 1 clinical diagnosis and which was known in the literature to be associated with elevated ESR were categorised as mixed diagnoses. When disease name was not specified, the diagnosis was categorised as unknown.

The data were computed using Microsoft excel 2010 and by descriptive statistics the total numbers, mean value and percentage of different groups were calculated. The aim was to study the common etiologies of EEESR in Indian patients at a tertiary hospital.

RESULTS

Table 1: Etiology of extremely elevated ESR with a gender distribution

Etiology	Male		Female		Total		Mean age of all patients
	N	%	N	%	n	%	
Infections	175	28.8	140	23.2	315	52	55
Renal	45	7.4	30	5	75	12.4	59
Malignancy	28	4.6	30	5	58	9.6	58
Miscellaneous	30	4.9	21	3.5	51	8.4	55
Mixed	30	4.9	16	2.7	46	7.6	55
Autoimmune	14	2.3	29	4.7	43	7	44
Unknown	13	2.1	6	0.9	19	3	60
Total	335	55	272	45	607	100	55

Within the broad categories of diseases, infection was the most common cause followed in descending order by renal diseases, malignancy, miscellaneous, mixed diagnoses, autoimmune diseases and unknown as summarised in the table 1.

Among the types of infection, the commonest was pneumonia followed by infected ulcers and urinary tract infections as shown in table 2.

Table 2: Extremely elevated ESR due to infections (n=315)

Type of infection	n	%
Pneumonia	73	23.17
Infected ulcers	61	19.36
Urinary tract infections	42	13.3
Sepsis	33	10.47
Osteomyelitis	28	8.8
Tuberculosis	24	7.6
Abscess	18	5.7
Cellulitis	10	3.17
Leptospirosis	9	2.95
Septic arthritis	8	2.5
Other infections	9	2.95

Other infections in 9 patients included 3 cases of HIV infection, 3 cases of Hansen's disease with one each case of Malaria, Rickettsia and Dengue.

The second most common diagnostic category were renal diseases. Among the types of renal diseases, chronic kidney disease was the most common as shown in table 3.

The third most common diagnostic category was malignancy. Non haematological malignancies namely carcinoma of solid organs was more common than haematological malignancies as summarised in table 4.

The fourth most common diagnostic category were the miscellaneous causes. In this category, traumatic causes were the commonest as shown in table 5.

During the study period, 607 patients had EEESR. There were 335 males and 272 females. The mean age was 55 years. The mean EEESR was 120mm/hr, highest being 180mm/hr and was seen in adenocarcinoma stomach with metastatic lymph nodes.

Table 3: Extremely elevated ESR due to renal causes (n=75)

Renal causes	n	%
Chronic kidney disease	40	53.3
Acute kidney injury	17	22.7
Acute kidney injury on chronic kidney disease	14	18.7
Glomerulonephritis	4	5.3

Table 4: Extremely elevated ESR due to malignancy (n=58)

Malignancies	n	%
Multiple myeloma	9	15.5
Leukemias *	6	10.3
MDS	1	1.7
Carcinoma lung	5	8.6
Carcinoma ovary	5	8.6
Others #	32	55.2

*Out of 6 cases of leukemias, 3 were acute myeloid leukemia, 1 each were chronic lymphocytic leukemia, acute lymphoblastic leukemia and chronic myelomonocytic leukemia.

#out of the 32 other cancers, 3 each were carcinoma colon, carcinoma breast, carcinoma stomach, carcinoma oesophagus, carcinoma cervix, carcinoma buccal mucosa.

2 each were carcinoma endometrium, carcinoma hypopharynx, 1 each were leiomyosarcoma uterus, carcinoma glottis, carcinoma prostate, carcinoma pancreas, carcinoma tongue, periampullary carcinoma, spindle cell sarcoma, carcinoma bladder, renal cell carcinoma, metastatic squamous cell carcinoma with unknown primary.

Table 5: Extremely elevated ESR due to miscellaneous causes (n=51)

Miscellaneous causes	n	%
Traumatic	16	31.3
Liver diseases	10	19.6
Venous thromboembolism	5	9.8
Ischemic heart disease	5	9.8
Severe anemia	4	7.9
others	11	21.5

Others include 3 each of pregnancy, endometriotic cyst, 2 each of heart failure, interstitial lung disease, 1 of acute ischemic stroke.

Table 6: Extremely elevated ESR due to autoimmune causes (n=43)

Autoimmune diseases	n	%
Rheumatoid arthritis	21	48.8
Systemic lupus erythematosus	12	27.9
Psoriasis	5	11.6
others	5	11.6

Others include 1 each of mixed connective tissue disease, vasculitis, autoimmune hepatitis, granulomatosis with polyangiitis, undifferentiated connective tissue disease.

The fifth most common diagnostic category in our study were mixed diagnoses. The EEESR in this category of patients could not be attributed to a single cause.

In this category there were 6 each of chronic kidney disease with pneumonia, chronic kidney disease with infected ulcers; 4 each of chronic kidney disease with rheumatoid arthritis, acute kidney injury with ulcer, 3 each of chronic kidney disease with pyelonephritis, urinary tract infections with pneumonia, Acute kidney injury with osteomyelitis; 2 each of chronic kidney disease with Tuberculosis, Chronic kidney disease with liver disease and ischemic heart disease, liver disease with pneumonia, fracture with chronic kidney disease, 1 each of tuberculosis with HIV infection, chronic kidney disease with metastatic lymph node with unknown primary.

The sixth most common diagnostic category was autoimmune diseases, with rheumatoid arthritis being the commonest in this category as shown in table 6. Unknown causes comprised 19% of all cases.

DISCUSSION

EEESR is a sensitive indicator of disease and is associated with a positive predictive value of 90% when correlating with certain diagnosis (9). To our knowledge this is the first study on frequency of diseases with EEESR in Indian population.

In an initial study done by Zacharski *et al.*, found that malignancy was the commonest etiology for EEESR constituting 58% of cases (10). In another study done by Stein and Xavier found inflammatory diseases as

the commonest cause constituting 71% of the cases (11). In another study done by Ohta *et al.*, on Japanese patients found inflammatory disease namely pseudogout as the commonest etiology for EEESR (4). However various studies have found infection as the commonest cause for EEESR followed by collagen vascular diseases and malignancy (6,7).

Similar to previous studies, we found 97% of patients had a known clinical diagnosis indicating that a severe disease is usually associated with EEESR and that infection was the commonest etiology (6,7). In the study done by Yousuf *et al.*, on Saudi patients reported infection as the commonest etiology with osteomyelitis being the frequent cause (6).

Compared to our study, data from patients examined at Mayo Clinic, Minnesota too detected infection as the commonest cause with pneumonia being common in this category. Our study too had 23.17% of pneumonia. The possible explanation could be pneumonia being commonest cause of morbidity and mortality in Indian population with increased incidence in elderly adults. Aging affects immune function and thereby making the older individuals susceptible for infection. This finding is also related to increased rates of smoking and alcoholism together with cumulative effects of co-morbid chronic diseases like COPD, Diabetes mellitus, Hypertension and their long-term treatment seen in these patients (12). In addition, advanced diagnostic and therapeutic protocols have led to increase in prevalence of these chronic diseases along with emergence of multidrug resistant organisms which poses an increased risk in these patients (7, 12).

The other main infections in our study were infected wounds and urinary tract infections. Most of the infected wounds comprised of infected skin ulcers in diabetic patients. This could be attributed to the fact that patients with Diabetes mellitus are prone to severe foot infections due to neuropathy and vascular dysfunction (13). Supporting this concept is previous research done by Hadavand *et al.*, indicating that the ESR in patients with infected ulcers was significantly higher than that of patients with non-infected diabetic ulcers (13).

Renal diseases were second most common cause for EEESR in our study. This result is unlike previous studies where renal diseases were either fourth or fifth cause for EEESR. This result could be attributed to the fact that our hospital being a tertiary referral centre has a nephrology unit which caters to patients with renal diseases. The most common renal associated diagnoses in our study were chronic kidney disease, acute kidney injury, acute kidney injury on chronic kidney disease which is similar to previous studies. These diseases are frequent causes for EEESR and therefore ESR may not always serve as an indicator of infections which is frequently seen in these patients (5,14). A study done by Al-Homrany indicated that

fibrinogen was the only factor which correlated significantly and independently with ESR. Compared to healthy controls, uremic patients had significant increase in quantity and activity of fibrinogen (5).

The third leading cause for EEESR in our study was malignancy. Non haematological malignancy being more common comprising 72.4% of all malignancies. This is different from the results previously reported. In a study by Yousuf *et al.*, done on Saudi patients, haematological malignancy namely lymphoma, multiple myeloma and leukemia were the most common malignancies associated with EEESR (6).

In another study done by Haque *et al.*, reported haematological malignancies as the only cause for EEESR in this category (3).

Our results indicated that carcinoma of solid organs was frequent etiology for EEESR with Carcinoma lung and carcinoma ovary being more common. An ESR of 100 and above usually indicates metastasis in patients with solid tumors. The high ESR in these patients has a poor prognosis (15,16). ESR however should not be used as a screening test for malignancy as the sensitivity of an EESR for malignancy is low (9,11,14).

Among haematological malignancies, myeloma comprised 15.5% of all the cases. Myeloma is known to have a strong association with raised ESR wherein clonal proliferation of plasma cells secrete immunoglobulins leading to plasma hyper viscosity (17).

However, unlike previous studies, our study failed to identify even a single cause of lymphoma for EEESR in this category. EEESR in Hodgkin's Lymphoma is a predictor of early relapse. The rates of elevated values of ESR reflect the course of disease and response to treatment in these patients (18).

Our study had 8.4% of miscellaneous causes for EEESR. Commonest etiology in this category was trauma induced by accidents, fractures and surgical operations. In a study done by Garnavos *et al.*, revealed that intramedullary nailing following fractures causes significant inflammatory reaction thereby causing sharp rise in ESR postoperatively. ESR often increases to high levels after major surgeries or extensive trauma and usually returns to normal within 6 months (19). Liver diseases were second most common in this group. The possible explanation for this is alcoholic liver cirrhosis being the commonest cause of chronic liver disease in India (20,21). Chronic alcohol consumption is associated with inflammation. Alcohol has adverse effect on haematopoiesis contributing to macrocytosis and anemia thereby causing further increase in ESR (20, 21).

Our study had 7.6 % of mixed diagnoses. These patients had more than 1 clinical diagnosis which was

known in the literature to be associated with elevated ESR. The association of chronic kidney disease with infection was more common in this category. This supports the concept of previous studies which report that infection is often co-existent with other diseases in patients with EEESR and that multimorbidity is a risk factor (6, 7). One of the patients in our study who had chronic kidney disease was diagnosed with metastatic lymph node of unknown primary and therefore malignancy can be easily overlooked in this rare occurrence.

Autoimmune diseases attributed to 7% of cases. The commonest etiology in this category being rheumatoid arthritis. This is in agreement with other similar studies. The EEESR in these patients indicates a state of heightened systemic inflammation and disease flare. EEESR may also signal heart failure in these patients (22). Second commonest etiology was systemic lupus erythematosus (SLE). In a study done by Firooz *et al.*, ESR levels did not differ significantly between patients with disease flare and active infection (23).

Strength of the study

To our knowledge this is the first study where we have tried to identify the causes of EEESR in Indian population in a tertiary care setting.

CONCLUSION

Our study reaffirms findings indicating that most patients have an underlying cause for EEESR and that infection is the commonest etiology in Indian patients. Mere finding of EEESR should not trigger expensive investigations and that widely available tests along with meticulous physical examination will help in reaching a diagnosis.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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