

## Diseases With Extremely Elevated Erythrocyte Sedimentation Rates in a Secondary Healthcare Facility: Retrospective Cohort Study

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**Background:** There is no data about the frequency of diseases with extremely elevated erythrocyte sedimentation rate (ESR) in secondary healthcare facilities in Japan.

**Methods:** We conducted a retrospective cohort study in Unnan City hospital in Shimane Prefecture to find out the frequency of diseases with ESR of more than 100 mm at one hour in a secondary healthcare facility in Japan. We gathered information on patients at the outpatient and emergency outpatient departments at the time of arrival and their final diagnosis.

**Results:** The total number of participants was 56, consisting of 19 men and 37 women. The average age recorded was 77.8 years. There were 30 cases (53.6%) of NIID (Non-infectious inflammatory disease), 10 cases (17.9%) of infectious diseases, 10 cases (17.9%) of malignancy, 2 cases (3.6%) of other diagnoses, and 4 cases (7.1%) of unknown diagnoses. The most prevalent disease among patients with ESR of more than 100 mm at one hour was pseudogout.

**Conclusion:** There may be specific prevalence of the diseases with ESR of over 100 mm at one hour in rural hospitals. In diagnosing the patients showing extremely high ESR, It may be important to consider the possibility of the specific diseases in rural hospitals in Japan.

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**Key words:** erythrocyte sedimentation rate, rural hospital, pseudogout

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## INTRODUCTION

Erythrocyte sedimentation rate (ESR) is a test that measures the rate at which erythrocytes settle in a test tube, within a period of one hour [1]. The main determinants of ESR are degree of red blood cell aggregation and hematocrit. Red blood cell aggregation is influenced by plasma proteins, which reduce the negative electrostatic forces between red cells, causing aggregation and faster sedimentation. The plasma proteins known as acute phase reactants include highly asymmetric molecules that are particularly effective in facilitating erythrocyte aggregation. Among these proteins are immunoglobulins, fibrinogen and main clotting proteins. High ESR may be an indication for chronic inflammation. Although it is insufficient on its own to make a definite diagnosis, it is useful as a screening test for fevers and indefinite diagnoses and for regular follow-up of chronic inflammatory diseases [1-3]. If ESR is over 100 mm at one hour in patients with fever of an unknown origin, range of differential diagnosis may be limited.

According to data obtained from a study of patients with ESR of over 100 mm at one hour in one tertiary healthcare facility, malignancy (lymphoma, myeloma, metastatic colorectal cancer, or metastatic breast cancer) constituted 58% of cases, whilst infectious or inflammatory diseases constituted 25%, many of which were infectious endocarditis, rheumatoid arthritis, or giant cell arteritis [4].

In another study conducted at the emergency outpatient unit of a tertiary healthcare facility, 4.2% of the total population demonstrated ESR of over 100 mm at one hour. Of these cases, infectious disease constituted 33% of cases, malignancy and kidney

disease 17%, and inflammatory disease 14% [5]. Currently, there are no data about the frequency of diseases with extremely high ESR in rural hospitals in Japan. Therefore, the purpose of this study was to investigate diseases with extremely high ESRs in our hospital in a Japanese rural area.

## METHODS

### *Research method:*

We conducted a retrospective cohort study. The study examined the records of patients who had attended Unnan City Hospital from April 2011 to March 2016 and had ESR of more than 100 mm at one hour at the time of arrival. Their final diagnoses and disease categories were also recorded.

### *Participants:*

This study included the records of all patients from April 2011 to March 2016, whose ESR was at the time of arrival found to be more than 100 mm at one hour at the outpatient and emergency outpatient departments.

### *Institution:*

The study was conducted at Unnan City Hospital in Unnan City, Shimane Prefecture. Unnan City is located in the eastern part of Shimane prefecture and the southern part is in contact with Hiroshima prefecture in Japan (Fig. 1). The total area of the land is 553.1 km<sup>2</sup>, accounting for 8.3% of the total area of Shimane prefecture, most of which is forestland. A survey conducted in 2015, revealed that the total population of Unnan city was 39,032 (consisting of 18,647 males, 20,385 females). Unnan City Hospital is the only public general hospital in Unnan City.

By March 2015, full-time doctors practiced in the following departments: internal medicine, surgery, orthopedics, pediatrics, dermatology, urology, otolaryngology, obstetrics and gynecology, general medicine. The yearly average of the number of outpatients from April 2011 to March 2016 was 101,891. In 2015, the number of outpatients who attended the various clinics were as follows: internal medicine; 4,530, surgery; 2,872, orthopedics; 3,744, pediatrics; 3,180, dermatology; 3,071, otolaryngology; 1,019. Although a secondary healthcare facil-

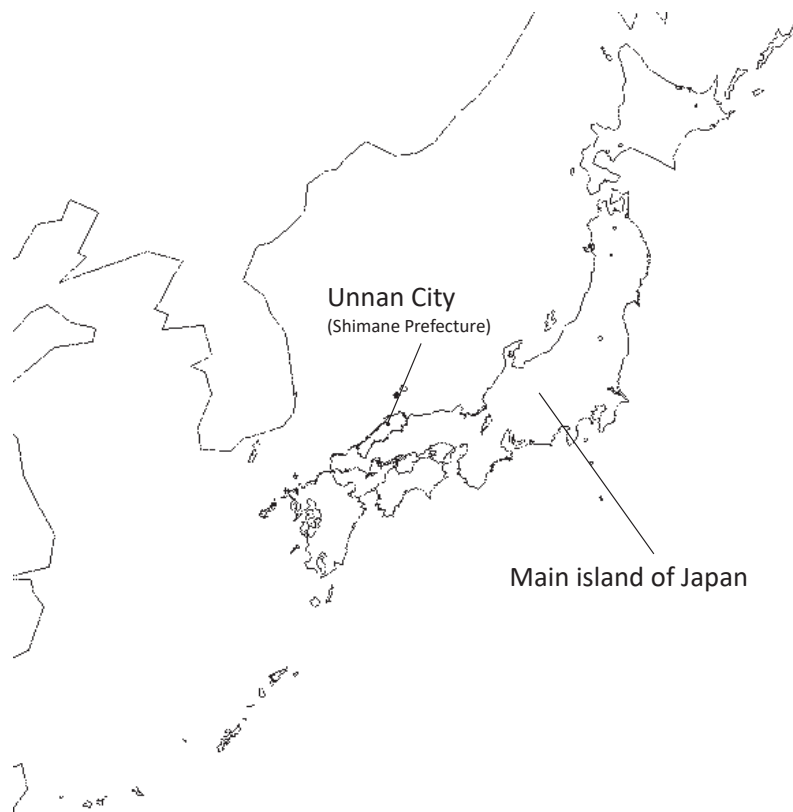


Fig. 1. Geographic location of Unnan City in main island Japan.

ity, our hospital still provides primary healthcare to patients, just like it used to, since the beginning of its operation. In 2015, 389 cases from the Department of Internal Medicine were submitted at the outpatient unit for ESR determination. The following are the number of submissions from the other departments: 893 cases from orthopedics, 4 cases from surgery, 3 cases from dermatology, and 6 cases from general medicine. ESR was measured by using Wintrobe method, in which venous blood is extracted in a tube containing 0.5ml of sodium citrate and stand vertical and the distance of fall of erythrocyte in one hour is expressed as ESR. It was performed in Unnan City Hospital.

#### **Data collection:**

Patient information was obtained from the electronic medical records of Unnan City Hospital from April 2011 to March 2016. We gathered information on patients who demonstrated ESR of more than 100 mm at one hour upon arrival at the outpatient and emergency outpatient departments. All relevant information on the patient, including age, sex, disease condition, and medical department in charge, were collected. We obtained the patient's diagnosis from the medical records; in some cases, the diagnosis was categorized as "unknown" where the disease name was not specified. We counted the multiple data from the same patients as a single data. Age, sex, name of diagnosis, charged department and value of ESR were collected by doctors on duty at Unnan City Hospital. This retrospective cohort study was carried out on the data provided by the clinical departments. Included in this data were records of cases with ESR greater than 100 mm at one hour at the time of arrival, along with the final diagnoses. Using a previous similar study as reference [6], we classified disease diagnoses into 5 categories: malignancy, infectious disease, non-infectious inflammatory disease (NIID), others, and unknown. We categorized hematological diseases except for lymphoma and leukemia as others. Primary macroglobulinemia contained Waldenstrom macroglobulinemia and IgM monoclonal gammopathy of undermined significance.

#### **Ethical consideration:**

The hospital was assured of the anonymity and confidentiality of patients' information. The contact information of the representative of the hospital was listed, such that it was possible to answer any questions about this research at any time. This study was approved by the Clinical Ethics Committee of Unnan Hospital.

## RESULTS

The number of ESR from April 2011 to March 2016 was 554, 589, 940, 992, 1295 prospectively. The total number of participants was 56 (9 cases in 2011, 7 cases in 2012, 10 cases in 2013, 13 cases in 2014, 17 cases in 2015). It consists of 1.3% of total number of ESR in 5 years. Man to woman ratio was 19:37. The average age of the participants was 77.8 years.

Twenty-four diseases showed ESR of more than 100 mm at one hour. There were 30 cases (53.6%) of NIID, 10 cases (17.9%) of infectious diseases, 10 cases (17.9%) of malignancy, 2 cases (3.6%) of other diagnoses, and 4 cases (7.1%) of unknown diagnoses (Fig. 2). Category and categorized diseases were showed in table 1. Among these were 14 cases of pseudogout, 8 cases of rheumatoid arthritis, 4 cases of primary macroglobulinemia, 4 cases of unknown, and a case of other disease (Table 2). In the cases of pseudogout, 13 cases were diagnosed by proving the existence of calcium pyrophosphate dehydrate (CPPD) in the fluid of joints and negative cultures of it. 3 cases of pseudogout were diag-

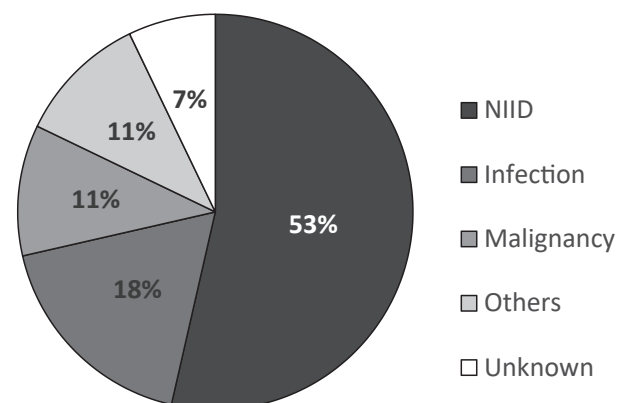


Fig. 2. Categories of diseases with ESR of more than 100 mm/hour. NIID: Non-infectious inflammatory disease.

Table 1. Categories and categorized diseases

<b>NIID (n=30)</b>
Pseudogout (14)
Rheumatoid arthritis (8)
Polymyalgia rheumatica (2)
Autoimmune hepatitis (1)
Behcet's disease (1)
Chronic thyroiditis (1)
IgG4 related disease (1)
Diffuse panbronchiolitis (1)
Nonspecific Interstitial pneumonia (1)
<b>Infection (n=10)</b>
Bacterial pneumonia (2)
Tuberculous pleuritis (2)
Pyogenic spondylitis (2)
Pulmonary tuberculosis (1)
Psoas abscess (1)
Non-tuberculous mycobacterial disease (1)
Pelvic abscess (1)
<b>Malignancy (n=10)</b>
Primary magroglobulinemia (4)
Gastric cancer (2)
Lung cancer (2)
malignant lymphoma (1)
malignant pleuritis (1)
<b>Others (n=2)</b>
Primary Lambert-Eaton myasthenic syndrome (1)
Primary myelofibrosis (1)
<b>Unknown (n=4)</b>

nosed as crown dens syndrome by proving calcification around dens of second cervical vertebra. In the case of nonspecific interstitial pneumonia, physicians ruled out infectious and autoimmunological etiologies. In cases of Primary Lambert-Eaton myasthenic syndrome, physicians performed laboratory tests, full body computer tomography and central spinal fluid test in order to rule out malignant etiologies, and there are no malignancies.

In cases of rheumatoid arthritis, specialists ruled out vasculitis and adult onset Still's disease by patients' symptoms and laboratory tests. In the cases of malignancy, physicians ruled out infections and other NIID by checking physical examinations, laboratory tests and blood cultures.

The number of patients with elevated ESR of more than 100 mm at one hour, provided by each department of medicine was 33 for internal medicine, 18 for orthopedic surgery, and less than 2 for other clinical departments (Fig. 3).

Table 2. Number of cases of each disease with ESR of more than 100 mm/hour

Disease	cases	ESR mean (min-max)
Pseudogout	14	116 (103-129)
Rheumatoid arthritis	8	110.1 (101-136)
Primary macroglobulinemia	4	127 (109-145)
Unknown	4	139.3 (122-146)
Lung cancer	2	109 (100-118)
Polymyalgia rheumatica	2	116.5 (111-122)
Bacterial pneumonia	2	108 (106-112)
Gastric cancer	2	135.5 (101-170)
Tuberculous pleuritis	2	105 (102-108)
Pyogenic spondylitis	2	116.5 (108-133)
Autoimmune hepatitis	1	133
Pulmonary tuberculosis	1	123
Psoas abscess	1	105
Nonspecific interstitial pneumonia	1	149
Primary Lambert-Eaton myasthenic syndrome	1	108
Behcet's disease	1	111
Malignant pleuritis	1	112
Malignant lymphoma	1	110
Diffuse panbronchiolitis	1	120
Non-tuberculous mycobacterial disease	1	133
Pelvic abscess	1	112
Primary myelofibrosis	1	115
Chronic thyroiditis	1	131
IgG4 related disease	1	129

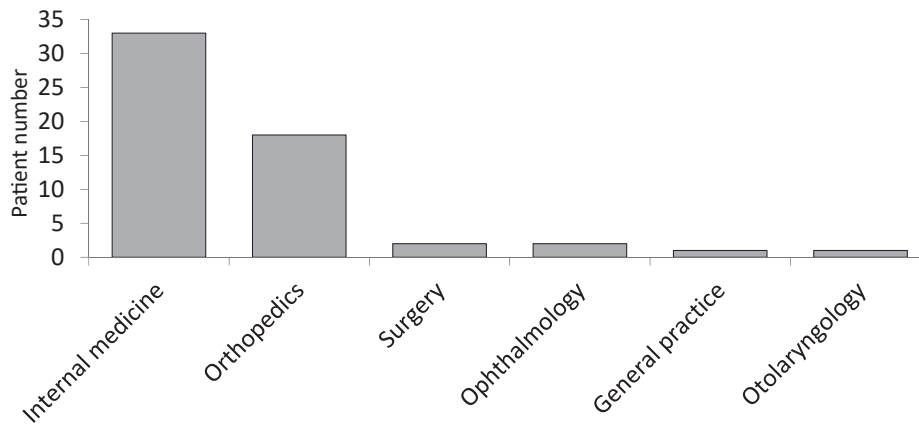


Fig. 3. Number of cases with ESR of more than 100 mm/hour, presented from each clinical department.

## DISCUSSION

In this study, the most prevalent disease in our hospital with elevated ESR of more than 100 mm at one hour was found to be pseudogout and the frequency of diseases with elevated ESR of more than 100 mm at one hour in this study was different from the results previously reported [4, 5]. At first, this may be attributed to the function of the hospitals since our hospital provides not only secondary care but also primary care in the area. Additionally, it might be related to the number of outpatient departure in orthopedics. In our hospital, the number of outpatient departure in orthopedics was the second large, it might lead to increase of patients with joint pain and pseudogout which is a common reason of arthritis in elderly.

It has been reported that in pseudogout, ESR is abnormally high, on average rising to about 70-80 mm/h [6]. Pseudogout is one of the highly inflammatory forms of arthritis associated with the release of pro-inflammatory cytokines such as interleukin-1 (IL-1), through a variety of pathways including the activation of inflammasomes in neutrophils, macrophages and other cell types. Additionally, the release of interleukin-6 (IL-6) may be especially increased in pseudogout [8]. IL-6 is known to stimulate B cell, T cell, neutrophil and macrophage, and mediate acute inflammation, which can lead extremely high ESR. Release of IL-6 from synoviocytes and monocytes is stimulated by CPPD crystals which often deposit in the joints of patients with pseudogout [8-

10].

Pseudogout can show inflammatory symptoms in various joints and be one of fever of unknown origin in the elderly. In cervical pseudogout, also referred to as crown dens syndrome, inflammation may occur in the joint, which may cause pain in both shoulders. There are some kinds of diseases showing bilateral neck pain and shoulder pains. For example, rheumatoid arthritis and polymyalgia rheumatica may show those symptoms and the clinical course can be from acute to subacute. It may therefore be difficult to distinguish from other rheumatic diseases [11]. In the cases, physician's interviews and physical examinations may support diagnosing such diseases.

In this study, patients with malignancy, chronic thyroiditis and myelofibrosis also showed extremely high ESR. In the pathophysiology of elevation of ESR, immunoglobulin has important role. In malignancy, IgG has shown to be increased, rarely to 100, but the amount not related to whether or not there was metastasis [12, 13]. In the pathogenesis of chronic thyroiditis, serum thyroid peroxidase antibody (TPO antibody) increases gradually [14]. TPO antibody is one of immunoglobulins, which might be the cause high elevated ESR in the disease [15]. In myelofibrosis, there is a possibility that it may be triggered by infections, neoplasms, and autoimmune diseases. Secondary myelofibrosis is known as one of the complications of SLE, which may present like primary myelofibrosis [16]. How-

ever, in this study, a patient was diagnosed with primary myelofibrosis, as the patient did not express any clinical expressions of SLE. In primary myelofibrosis, autoimmune may be involved and lead to increase in serum IgG and IgG4, which might be the cause high elevated ESR [17, 18].

ESR could be as useful as CRP in several situations. ESR has been suggested to be a more sensitive marker of acute inflammation than CRP to detect and monitoring the acute phase response after 24 hours [19, 20]. It has been also reported that CRP and ESR in infections commonly drop within 5 days in the process of recovery but in malignancy these may be constant, which can lead to the possibility of evaluating whether it is due to infection or malignancy by monitoring the discrepancy between changes in CRP and ESR as well as patients' symptoms [21]. ESR can be used for differential diagnosis of fever of indefinite complaints and some psychiatric disorder such as depression, chronic fatigue and syndrome [22, 23]. We may be able to narrow down the differential diagnosis by assessing the presence of inflammation with ESR such as malignancies [24]. Regarding the use of ESR in our hospital, most cases were examined by physicians and orthopedic surgeons, and the frequency of use of ESR was greatly influenced by the department in charge. All clinical departments may encounter infection and malignancy. It has therefore been suggested that ESR be employed to help effectively diagnose conditions, thereby ensuring a more effective treatment approach [25].

A limitation to this research was that there was the difference in number of ESR ordered among clinical departments. In this research, physicians of internal medicine and orthopedics mainly ordered a lot of. This may be attributed to the fact that ESR is a non-specific test and therefore, its choice depends on the depth of knowledge and experience of each physician and department. Moreover, the accuracy of the differential diagnosis also depends on the physician's ability. In this study, in a bid to reduce any errors, we examined all ESR results from our hospital within the last 5 years, and included as many medical departments and physicians as much as possible.

## CONCLUSION

NIID constituted half of the diseases with ESR of more than 100 mm at one hour. The most common disease recorded was pseudogout. When physicians use ESR in rural hospitals and encounter the very high value, they should take the difference in prevalence of the diseases with high value of ESR into consideration.

## REFERENCES

- 1) Brigden ML. The erythrocyte sedimentation rate: still a helpful test when used judiciously. *Postgrad Med* 1998;103:257-74.
- 2) Cantini F, Salvarani C, Olivieri I, *et al.* Erythrocyte sedimentation rate and C-reactive protein in the evaluation of disease activity and severity in polymyalgia rheumatica: a prospective follow-up study. *Semin Arthritis Rheum* 2000;30:17-24.
- 3) Van der Heijde DM, Van 't Hof MA, Van Riel PL, *et al.* Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis* 1990;49:916-20.
- 4) Zacharski LR, Kyle RA. Significance of extreme elevation of erythrocyte sedimentation rate. *JAMA* 1967;202:264-6.
- 5) Fincher RM, Page MI. Clinical significance of extreme elevation of the erythrocyte sedimentation rate. *Arch Intern Med* 1986;146:1581-3.
- 6) Naito N, Torikai K, Mizooka M, *et al.* Relationships between causes of fever of unknown origin and inflammatory markers: a multicenter collaborative retrospective study. *Intern Med* 2015;54:1989-94.
- 7) Busso N, So A. Microcrystals as DAMPs and their role in joint inflammation. *Rheumatology (Oxford)* 2012;51:1154-60.
- 8) Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum* 2011;63:3136-41.
- 9) Tagoe CE, Raza Y. Differences in acute phase reactants between gout and pseudogout. *Int J Clin Med* 2013;4:13-9.

- 10) Guerne PA, Terkeltaub R, Zuraw B, Lotz M. Inflammatory microcrystals stimulate interleukin-6 production and secretion by human monocytes and synoviocytes. *Arthritis Rheum* 1989;32:1443-52.
- 11) MacMullan P, McCarthy G. Treatment and management of pseudogout: insights for the clinician. *Ther Adv Musculoskelet Dis* 2012;4:121-31.
- 12) Mönig H, Marquardt D, Arendt T, Kloehn S. Limited value of elevated erythrocyte sedimentation rate as an indicator of malignancy. *Fam Pract* 2002;19:436-8.
- 13) Wu C, Lui W, Peng F, Wang SR. Alterations of humoral immunity in patients with gastric cancer. *Asian Pac J Allergy Immunol* 1988;6:7-10.
- 14) Sweeney LB, Stewart C, Gaitonde DY. Thyroiditis: an integrated approach. *Am Fam Physician* 2014;90:389-96.
- 15) Savas E, Sahin AZ, Aksoy SN, Tascan A, Sayiner ZA, Ozkaya M. Serum levels of inflammatory markers in patients with thyroid dysfunction and their association with autoimmunity status. *Int J Clin Exp Med* 2016;9:4485-90.
- 16) Pundole X, Konoplev S, Oo TH, Lu H. Autoimmune myelofibrosis and systemic lupus erythematosus in a middle-aged male presenting only with severe anemia: a case report. *Medicine* 2015;94 (19):e741. doi:10.1097/MD.0000000000000741.
- 17) Vergara-Lluri ME, Piatek CI, Pullarkat V, et al. Autoimmune myelofibrosis: an update on morphologic features in 29 cases and review of the literature. *Hum pathol* 2014;45:2183-91.
- 18) Bose P, Verstovsek S. The evolution and clinical relevance of prognostic classification systems in myelofibrosis. *Cancer* 2016;122:681-92.
- 19) Start J, Whicher JT. Test for detecting and monitoring the acute phase response. *Arch Dis Child* 1988;63:115-7.
- 20) Katz PR, Karuza J, Gutman SI, Bartholomew W, Richman G. A comparison between erythrocyte sedimentation rate (ESR) and selected acute-phase proteins in the elderly. *Am J Clin Pathol* 1990;94:637-40.
- 21) Kallio R, Bloigu A, Surcel HM, Syrjälä H. C-reactive protein and erythrocyte sedimentation rate in differential diagnosis between infections and neoplastic fever in patients with solid tumors and lymphomas. *Support Care Cancer* 2001;9:124-8.
- 22) Oliver B. Psychogenic fever, functional fever, or psychogenic hyperthermia? *Temperature* 2015;2:324-5.
- 23) Oka T. Psychogenic fever: how psychological stress affects body temperature in the clinical population. *Temperature* 2015;2:368-78.
- 24) Bolayirli M, Turna H, Orhanoğlu T, Ozaras R, Ilhan M, Ozgüroğlu M. C-reactive protein as an acute phase protein in cancer patients. *Med Oncol* 2007;24:338-44.
- 25) Dinant G, Knottnerus A, Van Whersch J. Leucocyte count as an alternative to ESR in general practice? *Scand J Prim Health Care* 1991;9:281-4.