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Disease Diagnosis Distribution in Patients with Anemia and Elevated Sedimentation Above 50 mm/hr: A Single-center Experience

Anemi ve 50 mm/saat Üzerinde Sedimentasyon Yüksekliği Olan Hastalarda Hastalık Tanı Dağılımı: Tek-merkez Deneyim

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ABSTRACT

Background: Erythrocyte sedimentation rate (ESR) is a simple and inexpensive blood test with low sensitivity and specificity. However, it can be affected by many factors and there is no limit value valid for all patients. Anemia is also a phonemenon that should be investigated for many diseases. Sedimentation is a criterion in the diagnosis and follow-up of diseases in which both inflammation and autoimmunity are considered to be involved in the etiology, such as temporal arteritis and inflammatory bowel disease. A sedimentation rate of 50 mm/h or less is an exclusion criterion in vasculitis. In this study, we aimed to determine the distribution of disease diagnosis in patients with elevated sedimentation above 50 mm/h and anemia.

Materials and Methods: Ethics committee approval numbered B.30.2.PAÜ.0.20.05.09/187 was obtained for the study. The data of 300 patients with anemia and elevated sedimentation who were admitted to the Outpatient Clinic of Pamukkale University Hospital Internal Medicine and related subspecialties and who were hospitalized in the wards of Pamukkale University Hospital Internal Medicine and related subspecialties between November 2011 and November 2012 were retrospectively analyzed.

Results: A total of 300 patients with ESR exceeding 50 mm/h and anemia were identified. Of the patients, 154 were female (51.3%) and 146 were male (48.7%). The mean age of the women was 59.08±19.0 years and the mean age of the men was 62.4±14.1 years. The mean ESR was 77.55±21.21 mm/h in women and 82.89±19.24 mm/h in men. The mean hemoglobin was 10.31±1.60 g/dL in women and 10.69±1.52 g/dL in men. In the distribution according to disease groups, oncologic diseases had the highest rate (27.9%) and pulmonary diseases had the lowest rate (1%).

Conclusion: No difference was detected in the diagnostic distribution of the patients after lowering the lower limit of ESR to 50 mm/h compared to the literature. When the correlation between hemoglobin and ESR was examined, it was determined that ESR increased as hemoglobin decreased. We recommend differential diagnosis with further investigation especially in patients with high ESR accompanied by anemia.

Keywords: Anemia, cancer, erythrocyte sedimentation rate, inflammation, malignancy

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ÖZ

Amaç: Eritrosit sedimentasyon hızı (ESH) basit ve ucuz, ancak duyarlılığı ve özgünlüğü düşük bir kan testidir. Ancak birçok faktörden etkilenebilir ve herkes için geçerli bir sınır değeri yoktur. Anemi de birçok hastalık için araştırılması gereken bir bulgudur. Temporal arterit ve enflamatuvar bağırsak hastalığı gibi etiyolojisinde hem enflamasyonun hem de otoimmünitenin rol aldığı düşünülen hastalıkların tanı ve takibinde sedimentasyon bir kriterdir. Vaskülitlerde 50 mm/saat ve altında olması bir dışlanma kriteridir. Bu çalışmada 50 mm/saat üzerinde sedimentasyon yüksekliği ve anemisi olan hastalarda hastalık tanı dağılımını belirlemeyi planladık.

Gereç ve Yöntemler: Çalışma için B.30.2.PAÜ.0.20.05.09/187 sayılı etik kurul onayı alındı. Kasım 2011 ile Kasım 2012 arasında Pamukkale Üniversite Hastanesi İç Hastalıkları ve ilgili yan dallarının polikliniğine başvurmuş ve Pamukkale Üniversite Hastanesi İç Hastalıkları ve ilgili yan dallarının servislerinde yatırılarak takip edilen anemi ve sedimentasyon yüksekliği olan 300 hastanın verileri retrospektif incelendi.

Bulgular: ESH'si 50 mm/sa'yi geçen ve anemisi olan 300 hasta belirlendi. Hastaların 154'ü kadın (%51,3) 146'sı erkekti (%48,7). Kadınların yaş ortalaması 59,08±19,0 yıl, erkeklerin yaş ortalaması ise 62,4±14,1 yıl olarak tespit edildi. ESH kadınlarda ortalama 77,55±21,21 mm/sa, erkeklerde ise 82,89±19,24 mm/sa saptandı. Hemoglobin kadınlarda ortalama 10,31±1,60 g/dL, erkeklerde ise 10,69±1,52 g/dL saptandı. Hastalık gruplarına göre dağılımda en yüksek oranı onkolojik hastalıklar alırken (%27,9), en az hasta içeren grup ise göğüs hastalıkları (%1) olmuştur.

Sonuç: ESH alt sınırını 50 mm/sa'ye düşürmekle hastaların tanı dağılımında literatürle karşılaştırıldığında farklılık saptanmadı. Hemoglobin ile ESH arasındaki korelasyona bakıldığında hemoglobinin düştükçe ESH'nin arttığı saptandı. Özellikle yüksek ESH'ye aneminin eşlik ettiği hastalarda ileri tetkik ile ayırıcı tanının yapılmasını öneririz.

Anahtar Kelimeler: Anemi, kanser, eritrosit sedimentasyon hızı, enflamasyon, malignite

Introduction

The most valuable test in the determination of anemia is hemoglobin determination (1,2,3). According to the definition of the World Health Organization, anemia is defined as a hemoglobin level below 13 g/dL in men over the age of 15, 12 g/dL in women over the age of 15 who are not pregnant, and 11 g/dL in pregnant women (4).

The sedimentation rate is a diagnostic aid in many diseases. It is a blood test which is widely used, simple and results are obtained in a short time, but has low sensitivity and specificity (5,6,7,8). Erythrocyte sedimentation rate (ESR) displays a physiologic increase with age. It is measured higher in women than in men, in patients with hypercholesterolemia than in those without hypercholesterolemia and at low altitude than at high altitude (9,10). Commonly accepted reference values have been determined as 15 in men under the age of 50 years and 20 in women, 20 in men aged 50-85 years and 30 in women, and 30 in men over 85 years and 42 mm/h in women.

ESR is a helpful test for inflammatory, malignant and infectious diseases in the clinic and provides general information about body temperature, pulse and leukocyte count. In case of increased ESR, the patient's age, gender and medications should be taken into consideration.

ESR is one of the tests frequently utilized in the evaluation of acute phase response. Acute phase reaction includes events (inflammation, coagulation, complement activation, endothelial activation) characterized by the development of a number of simultaneous or successive reactions (inflammation, coagulation, complement activation, endothelial activation) with cytokines released from the responding cells (polymorph nucleated leukocytes, antigen presenting cells and endothelium) in the presence of a stimulus (11).

Stimuli (infection, trauma, immunologic/allergic reactions, surgical intervention, hypoxia, burn, malignancy) that lead to the development of an acute phase reaction cause tissue damage. Cytokine release occurs within 1-2 hours following the onset of inflammation, with the earliest response being neutrophilia and fever. Subsequently, serum iron and zinc levels decrease and the synthesis of some proteins in the liver is affected. When tissue damage occurs, especially serum fibrinogen, serum amyloid A protein and C-reactive protein (CRP) levels increase and albumin levels decrease. The increase in many asymmetric molecules such as fibrinogen and gammaglobulin accelerates erythrocyte aggregation. ESR increases. In our study, we evaluated the relationship between anemia and ESR.

Material and Methods

Ethics committee approval numbered B.30.2.PAÜ.0.20.05.09/187 was obtained for the study. The files of approximately 4.000 patients who were admitted to the Outpatient Clinics of Pamukkale University Hospital Internal Medicine and related subspecialties and who were hospitalized and followed up in the wards of Pamukkale University Hospital Internal Medicine and related subspecialties between November 2011 and November 2012 were retrospectively scanned in Probel HIS computer system. Those with ESR exceeding 50 mm/h and anemia were evaluated in accordance with the study criteria and

300 patients were included. If there was more than one ESR exceeding 50 mm/h during the measurements, the ESR with the highest value was recorded. The Hb level at the highest ESR value was recorded if it was below 13 g/dL in men and below 12 g/dL in women. Patients with ESR above 50 mm/h without anemia were excluded from the study. If there was more than one diagnosis, patients were enrolled in the most probable diagnostic groups that would increase ESR above 50 mm/h. The patient's age, gender, comorbidities, if any, medication use, ESR, hemoglobin level, bone marrow aspiration and biopsy, if any, and diagnosis were recorded.

Statistical Analysis

In the descriptive thesis, the data were evaluated in the SPSS 23.0 package program and the results were expresses as %, mean, and standard deviation. A p-value below 0.05 was considered significant.

Results

Of the 300 patients with anemia and ESR above 50 mm/h, 154 were female (51.3%) and 146 were male (48.7%) (Table 1). The mean age of the women was 59.08±19.0 years and the mean age of the men was 62.4±14.1 years. Demographic and laboratory findings of the patients are summarized in Tables 1, 2 and 3. Of the 300 patients, 130 (43.2%) had known chronic diseases while 170 (56.8%) had no known chronic disease. Of the 300 patients, 118 (39.3%) were taking medication while 182 (60.7%) were not. Fifty-one patients (17%) underwent bone marrow aspiration biopsy for further investigation and 22 patients (7.3%) had malign infiltration. According to the bone marrow infiltration of 22 patients, lymphoma in 10 patients, acute myeloblastic leukemia in 6 patients, acute lymphoblastic leukemia in 4 patients and Waldenström macroglobulinemia in 2 patients were diagnosed.

Table 1. Demographic information and comorbidities of patients

	Female	Male
Number of patients	154 (51.3%)	146 (48.7%)
Mean age	59.08±19.0 year	62.4±14.1 year
History of comorbidities		
• Diabetes mellitus type 2	24 (15%)	33 (22%)
• Hypertension	25 (16%)	24 (16%)
• Thyroid-related diseases	6 (3%)	1 (1%)
• Rheumatologic diseases	5 (3%)	Absent
• Coronary artery disease	5 (3%)	11 (7%)
• History of malignancy	3 (2%)	5 (3%)
• Congestive heart failure	2 (1%)	3 (2%)
• Inflammatory intestinal disease	Absent	2 (1%)
History of medication use	55 (35%)	63 (43%)

When age groups were analyzed, the highest number of patients were between the ages of 60-70 years (75 patients) and the lowest number of patients were between the ages of 15-30 years (19 patients). When ESR was compared between age groups, the highest ESR was found between the ages of 60-70 years. When the ESR of the patient group under 30 years of age was compared with the ESR of the patient groups aged 30-39, 40-49, 50-59, 60-69, 70-79 and 80-100 years, the ESR of the patients in the 40-49, 50-59, 60-69, 70-79 age groups was found to be significantly higher (p=0.01; 0.04; 0.04; 0.03). According to the diagnosis groups, the highest mean ESR value was observed in the oncologic patient group (Table 4).

In the distribution by disease groups, oncological diseases and malign hematological diseases had the highest proportion (27.9%), followed by infectious diseases (19.9%), nephrological diseases (13.3%), rheumatological diseases (10.6%), gastroenterological diseases (9.6%), cardiovascular diseases (7.3%), endocrinological diseases (2.7%), and benign hematological diseases (2.3%). The group with the least number of patients was pulmonary diseases (1%) (Figures 1, 2). 5% patients could not be included in any group. The highest ESR was 140 mm/h in a 21-year-old female patient with active ulcerative colitis. In males, the highest ESR of 140 mm/h was recorded in a 70-year-old patient with Waldenström Macroglobulinemia.

When the correlation between hemoglobin and ESR was examined, it was determined that ESR increased as hemoglobin decreased. Diagnosis groups were compared with each other in terms of ESR. ESR of malignancy patients was significantly higher than ESR of cardiology,

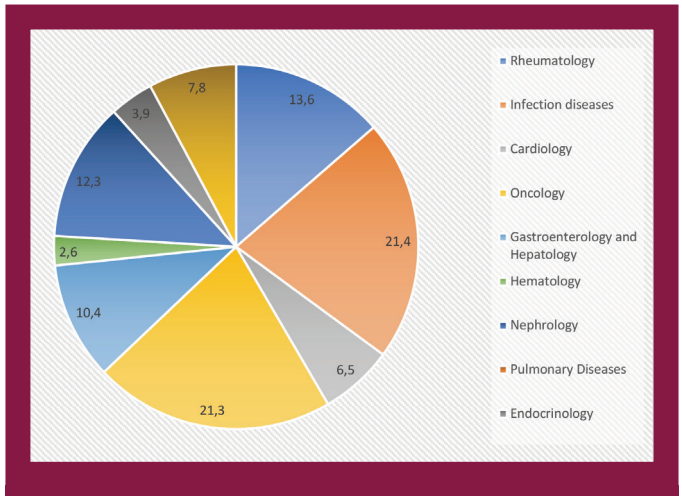

Figure 1. Distribution of patients by diagnostic group in females

gastroenterology and endocrinology patients (p=0.05; 0.01; 0.02).

We divided the patients into 4 groups according to anemia type. Patients diagnosed with hematologic malignancy were included in group 1, patients with iron deficiency anemia were included in group 2, patients with chronic disease anemia were included in group 3, and patients other than these anemias were included in group 4. The rates were 8.4% in group 1, 10.4% in group 2, 74.0% in group 3, and 7.1% in group 4 (Figure 3). In men, 6.2% in group 1, 7.5% in group 2, 84.2% in group 3, and 2.1% in group 4 (Figure 4).

Anemia types and ESR groups were compared and no significance was found between them (p=0.86). Albumin globulin ratio of 206 patients was analyzed. The number of female and male patients with an albumin globulin ratio below 1 was 34 and 49, respectively. There was a negative

Table 2. Biochemical and hematologic values of female patients included in the study

Laboratory data	Number of patients	Mean	Min	Max
White cell count (K/uL)	154	9.50±8.72	0,68	70,9
Neutrophil count (K/uL)	154	6.02±5.56	0,02	52,60
Lymphocyte count (K/uL)	154	2.23±3.99	0,29	40,09
Hb* (g/dL)	154	10.69±1.52	2,8	11,9
MCV* (%)	154	85.36±9.38	57	113
RDW* (%)	154	15.72±2.28	11,2	25
Ferritin (ng/mL)	94	339.65±502.43	2,4	2000
Vitamin B12 (pg/mL)	92	637.43±542.43	99,4	2000
Folic acid (ng/mL)	89	14.42±32.55	3,8	315
Albumin (g/dL)	147	3.44±0.65	2	5,2
Globulin (g/dL)	103	3.32±1	1,59	7,71
Albumin/globulin	103	1.11±0.37	0,16	2,36
C-reactive protein (mg/dL)	135	6.60±9.59	0,04	49
Blood urea nitrogen (mg/dL)	127	20.19±16.5	3	92
Creatinine (mg/dL)	145	1.13±1.21	0,29	6,3

*HB: Hemoglobin, MCV: Mean corpuscular volume, RDW: Red cell distribution width

Table 3. Biochemical and hematologic values of the male patients included in the study

Laboratory data	Number of patients	Mean value	Min value	Max value
White cell count (K/uL)	146	9.40±5.68	0.58	49.8
Neutrophil count (K/uL)	146	6.45±4.09	0.10	29.2
Lymphocyte count (K/uL)	146	1.88±3.39	0.19	42.2
Hb* (g/dL)	146	10.31±1.60	5.1	12,9
MCV* (%)	146	85.36±9.38	59	117
RDW* (%)	146	15.72±2.28	11.7	30
Ferritin (ng/mL)	85	435±461.51	2.2	2341
Vitamin B12 (pg/mL)	92	581.01±506.78	44	2000
Folic acid (ng/mL)	85	12.94±30.82	3.3	286
Albumin (g/dL)	148	3.38±0.69	1.88	4.95
Globulin (g/dL)	103	3.35±1.35	1.02	11.9
Albumin/globulin	103	1.09±0.37	0.16	2.13
C-reactive protein (mg/dL)	142	7.70±8.12	0	38
Blood urea nitrogen (mg/dL)	141	25.82±21.85	2	112
Creatinine (mg/dL)	148	1.64±1.79	0.4	8.4

*HB: Hemoglobin, MCV: Mean corpuscular volume, RDW: Red cell distribution width

correlation between albumin globulin ratio and ESR (Pearson correlation =-0.37 for women, Pearson correlation =-0.24 for men). There was a positive correlation between CRP and ESR (pearson correlation =0.19).

Discussion

Both ESR and hemoglobin values vary according to the age and gender of the patient (12). In the study of Aysalar et al. (13) including 500 patients, a very weak positive correlation was observed between age and ESR in all patients. It was found that ESR increased with a very weak correlation as age increased (r=0.186, p=0.0001). The correlation coefficient of this very weak relationship was r=0.182 (p=0.001) in women and r=0.170 (p=0.02) in men. A very weak correlation was determined between ESR and age in both genders (13). When ESR was evaluated according to age groups in our study, it was determined that ESR increased with increasing age in the ESR of the patient group up to the age of 70 years. ESR, which is expected to increase with increasing age, was determined to be lower in patients older than 70 years in our study compared to patients in the 15-69 age group.

Acceleration in ESR is more frequent in solid tumors than in hematologic malignancies. Lung, breast, colorectal and urinary system tumors are frequently associated with high ESR (14,15). In our study, the highest ESR was detected in the oncologic patient group and the lowest ESR was found in the pulmonology patient group.

Cengiz et al. (16) evaluated the distribution of disease diagnosis in 110 patients aged 65 years and older with ESR of 80 mm/h and above who were followed up in a geriatrics clinic. In the distribution by disease groups, infectious diseases had the highest proportion (48.2%) and oncologic diseases had the second highest proportion (17.3%). The most common infectious disease was

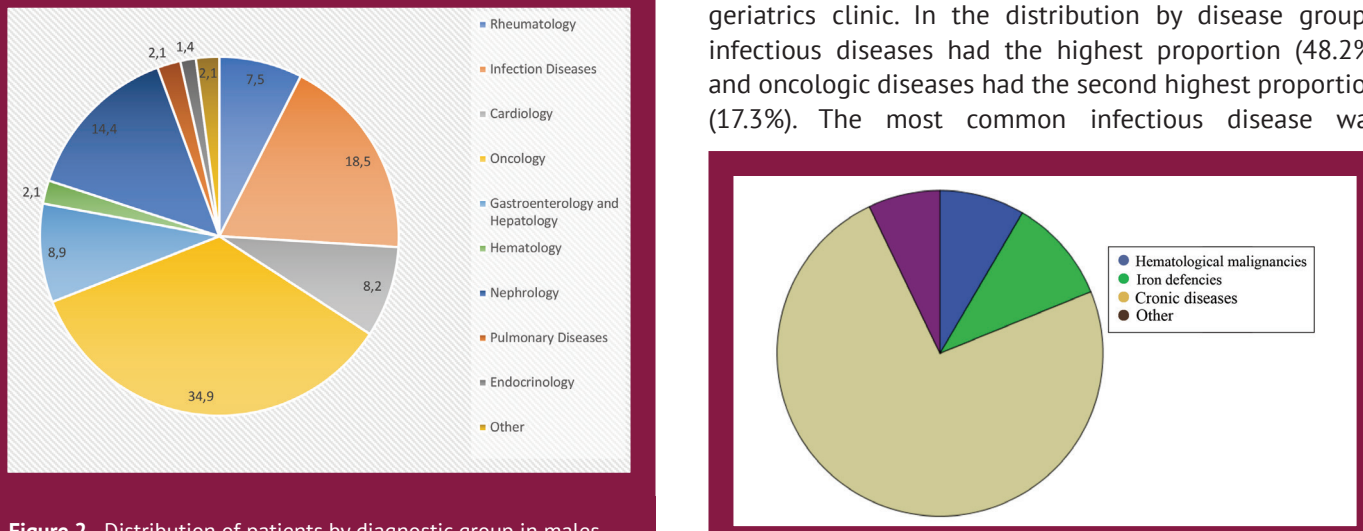

Figure 2. Distribution of patients by diagnostic group in males

Table 4. ESR according to diagnostic groups

	Mean value (mm/sa)	Min value (mm/sa)	Max value (mm/sa)
Rheumatic diseases	79.09±18.63	52	110
Infectious diseases	81.05±19.77	52	123
Cardiological diseases	72.55±18.07	52	116
Oncological diseases	86.46±21.40	52	140
Gastrointestinal and hepaticobiliary diseases	74.14±19.56	50	140
Hematologic diseases	69.57±21.18	52	115
Nephrological diseases	81.42±20.68	52	120
Pulmonary diseases	75.0±14.73	59	88
Endocrinologic diseases	72.25±19.6	53	99

Figure 3. Distribution of patients according to anemia type in females

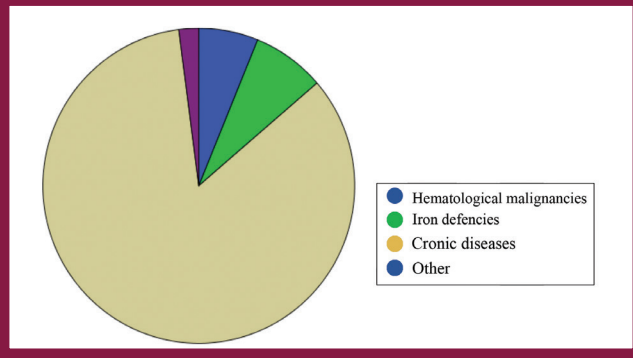

Figure 4. Distribution of patients according to anemia type in males

pneumonia with 37.7%. The most common malignancy was multiple myeloma with 32%. In our study, 16% of the patients had hypertension, 1.3% had coronary artery disease, 15% had type 2 diabetes mellitus and 56.8% had no known history of chronic diseases.

Haque et al. (17) evaluated 100 patients with ESR above 100 mm/h. The most common complaints of the patients were high fever, general malaise and pallor. While hematologic oncologic diseases were found in 41%, infectious diseases were detected in 36%. In our study, the most common complaint of the patients was fatigue with a rate of 30%.

Lluberas-Acosta and Schumacher (12) detected infection in 43, malignancy in 16, rheumatologic disease in 30, inflammatory disease in 7, renal dysfunction in 25 and diseases from different systems in 38 of 162 hospitalized patients with elevated ESR. Similarly, in a study conducted in Zimbabwe, infection was observed in 46, malignancy in 25, connective tissue disease in 17, kidney disease in 8 and liver disease in 5 of 101 patients with high ESR. In this study, pneumonia was found to be the most common infectious cause of elevated ESR, while multiple myeloma was the most common malignancy with the highest ESR (18). In our study, the highest ESR was found in patients diagnosed with ulcerative colitis and Waldenström Macroglobulinemia.

Kocabaş (19) of the 361 patients diagnosed with ESR above 100 mm/h, 41 (10.65%) had hematologic diseases and 146 (37.92%) had neoplastic diseases (including hematologic). Infectious diseases were detected in 172 (44.68%) patients, musculoskeletal and connective tissue diseases in 34 (8.83%) patients, chronic renal failure in 40 (10.39%) patients.

Baicus et al. (20), in a study conducted in Romania, determined that the likelihood of cancer increased with age in the presence of high ESR (>29 mm/h) and anemia; the positive predictive value was 64% and the negative predictive value was 91% in the presence of advanced age (>65), anemia and high ESR; neither age nor ESR nor anemia could rule out cancer, but they could increase the likelihood of cancer from 24% to 64% or decrease it from 24% to 9%.

Arvidson et al. (21) reported no correlation between daily activity score and ESR in patients with rheumatoid arthritis, but determined that CRP and fibrinogen levels were closely related and that fibrinogen determination would be more accurate than ESR in determining disease activity.

Bridgen (8) stated that ESR is still very useful when used meticulously; ESR above 100 mm/h is sufficiently sensitive, specific and significant and is related to a serious underlying disease with a 90% probability; in the presence of an extremely high ESR in an asymptomatic person, a conclusion can usually be reached with a few simple tests; if not, the test should be repeated after waiting a few months before starting very detailed and expensive examinations; and the use of ESR as a screening test would not be appropriate (22). In our study, ESR was detected to be 100 mm/h or above in 17.5% of women and 23.9% of men. Malignancy was detected in 48.1% and infection in 14.8% of 27 female patients with ESR ⩾100 mm/h. Among 35 male patients with ESR ⩾100 mm/h, 31.4% had malignancy and 28.5% had infection (23).

In vasculitis, a sedimentation rate of 50 mm/hour and below is an exclusion criterion (24). When the literature was reviewed, the lower limit value of ESR was determined as 100 mm/h in studies to determine the diagnostic distribution in patients with high ESR. In our study, the lower limit value of ESR was set as 50 mm/h, aiming to reach a wider patient group. Asymptomatic patients with anemia in addition to elevated ESR were included to exclude asymptomatic, unexplained patients with elevated ESR but followed up healthy patients. When compared with the literature, similar disease distributions were obtained. In the study by Sarı et al. (23) differently, in the distribution according to disease groups with ESR exceeding 100 mm/h, rheumatic diseases had the highest rate (30%) and cardiovascular diseases had the lowest rate (3%).

Baicus et al. (20) examined age, ESR and anemia values in 431 patients with weight loss. Cancer was diagnosed in 24% of the patients with further investigation. They recommended that patients with complaints of weight loss should be evaluated together with age, ESR and anemia and demonstrated the necessity of further examination in terms of cancer.

ESR is a diagnostic criterion in giant cell arteritis and polymyalgia rheumatica diseases and is always elevated in patients with giant cell arteritis, frequently above 90 mm/h (25,26). In our study, 1 patient was diagnosed with Polymyalgia Rheumatica and ESR was measured as 90 mm/h.

Gamaldo et al. (27) prospectively evaluated 827 patients aged 50-96 years with neurologic diseases such as cerebrovascular disease intermittently. High MCV levels were associated with significantly lower global mental status, long delayed memory and attention. Since the surface to volume ratio is small in macrocytic cells, erythrocytes collapse rapidly. In our study, a negative correlation was detected between hemoglobin and ESR. Anemia with elevated ESR was mostly a laboratory finding and was generally considered as an indicator of an underlying chronic disease.

Conclusion

ESR, especially excessive elevation is associated with many diseases, especially malignant diseases, infections and collagen tissue diseases. No difference was found in the diagnostic distribution of the patients after lowering the lower limit of ESR to 50 mm/h compared to the literature.

In our study, patients with ESR above 50 mm/h and anemia were included to exclude these patients. It was detected that anemia deepened as ESR increased. It was observed that ESR elevation was mostly accompanied by anemia of chronic disease. This indicates that anemia is a finding secondary to the disease causing ESR elevation.

ESR is a test with low specificity and sensitivity, although it is easy and inexpensive with quick results. Although it can still be useful in the provision of primary health care services in the diagnosis and follow-up of various diseases, it can lead to the performance of highly invasive tests, most of which are normal at high values. In this context, it is recommended that ESR is definitely not a screening test and in case of high values detected in asymptomatic individuals, after a detailed history and physical examination, it is recommended to proceed to further investigations starting with simple tests in patients who are still suspicious and who have anemia.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for the study from Pamukkale University, numbered B.30.2.PAÜ.0.20.05.09/187.

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.E.Ö., A.K., C.Ö., İ.S., S.H., İ.G., Concept: T.E.Ö., A.K., Design: T.E.Ö., A.K., C.Ö., İ.S., S.H., Data Collection or Processing: T.E.Ö., Analysis or Interpretation: T.E.Ö., C.Ö., İ.S., S.H., Literature Search: T.E.Ö., C.Ö., İ.S., S.H., İ.G., Writing: T.E.Ö., C.Ö., İ.S., S.H., İ.G.

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