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Etiological classification of high sedimentation rate and relation with other inflammatory markers

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Abstract

This study describes the causes of significantly increased erythrocyte sedimentation rate (ESR) and compares the etiological categories based on inflammatory markers. We collected data from the patients who applied between March 2020 and August 2023. Patients were categorized into five groups based on their identified etiology. Categories were sorted as infection, inflammatory, malignancy, renal, and others. Inflammation markers were compared between groups and ROC analysis was performed if there was a significant difference. The cause of the elevated ESR levels in 291 patients was determined. The median age was 58 (18-92). ESR levels were lower in females (113, 106-120) than in males (119, 109-120) (p=0.015). The distribution of etiological disease categories was as follows: inflammatory (41.9%), infection (35.1%), malignancy (18.2%), renal (3.1%), and others (1.7%). Albumin levels were lower in the malignancy group than in the inflammatory group (p<0.005). Platelet counts of the inflammatory group were higher than other groups (p=0.005). Neutrophil-lymphocyte ratio (NLR) was higher in the malignancy group than in the inflammatory group (p=0.001). Monocyte-lymphocyte ratio (MLR) was, NLPR, and SIRI were lower in the inflammatory group than others (p<0.001). ROC curves for inflammatory markers have been calculated. MLR had the highest area under the curve (AUC: 0.655, p<0.001), and the cut-off value of MLR which is 0.2775 had 65.3% sensitivity and 65.5% specificity to identify the cases without the inflammatory disease. This study presents the causes of significantly increased ESR and its correlation with inflammatory markers. We aim to highlight the differences between etiological groups using cost-effective and accessible blood test results.

Keywords: Erythrocyte sedimentation rate, inflammation, monocyte-lymphocyte ratio, neutrophil-lymphocyte platelet ratio, systemic inflammation response index

Introduction

The erythrocyte sedimentation rate (ESR) is a laboratory test that measures the aggregation of red blood cells in one hour and is interpreted as mm/hour. ESR is a widely used test in the general population; however, it lacks specificity for a specific disease category. Minor increases in ESR may occur without an illness; however, significant elevations are typically linked to infections, inflammations, and malignancies [1-5]. C-reactive protein (CRP) can be used to evaluate ESR for diagnostic purposes [6-8]. Erythrocyte sedimentation rate and CRP are valuable tools for physicians, although they are not sufficient for a full assessment of patients. Subsequent investigations depended mainly on expensive laboratory methods. Recent research has indicated a correlation between new inflammatory markers derived from whole blood cell counts and illnesses such as osteoporosis, cardiovascular mortality, cancer, and inflammatory diseases. No study has assessed these markers to differentiate the etiology of elevated ESR. These markers are primarily based on the whole blood cell count and other acute phase reactants such as albumin and CRP.

It aims to evaluate the diseases linked to an ESR above 100 mm/hour, classify the common etiologies, and use novel inflammation markers to differentiate them. This study shows the association with various novel inflammation markers such as Aggregate Index of Systemic Inflammation (AISI), Neutrophil-to-Lymphocyte ratio (NLR), Neutrophil to Lymphocyte Platelet ratio (NLPR),

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Platelet-to-Lymphocyte ratio (PLR), Monocyte-to-lymphocyte ratio (MLR), Systemic immune-inflammation index (SII), and Systemic Inflammation Response Index (SIRI).

Material and Methods

Patients

This study was conducted on patients who applied to the internal medicine outpatient or inpatient clinic of Istanbul Sancaktepe Şehit Prof. Dr. Ilhan Varank Training and Research Hospital between 1 March 2020 and 1 August 2023. Ethics committee approval was obtained from the Sancaktepe Şehit Prof. Dr. Ilhan Varank Training and Research Hospital ethical committee with decision number 2023/140. Patients over 18 years of age and with an ESR level higher than 100 mm/hour were included in the study. The patient's demographic characteristics, medical history, and blood test results were examined retrospectively through the hospital information management system. ESR was measured using Alifax Capillary Photometry Technology. If patients have a single measurement of high ESR, investigation of the etiology focused on the episode with simultaneous blood results. If patients have multiple results of ESR levels higher than 100 mm/hour, investigation of the results focused on the whole follow-up. The first blood sample with high ESR was analyzed for other test results for patients with multiple results of high ESR.

Patients were categorized into five groups based on their identified etiology. If the patient had multiple potential causes, another physician reviewed the patient's data and grouped it based on the most likely explanation. If the patient has a chronic disease but previous results are normal, the sudden episode of high ESR was attributed to a new ongoing reason. If the patient has a chronic disease and multiple high ESR levels and ESR levels were related to the severity of the disease, high ESR levels were attributed to chronic disease. Upon thorough investigation, categories were sorted as infection, inflammatory, malignancy, renal, and others. Inclusion criteria were being over 18 years old and having at least one result of ESR level higher than 100 mm/hour. Exclusion criteria included those under 18 years old, inadequate examination of the cause of high ESR, and no specific explanation for high ESR. Undiagnosed patients were excluded.

Measurements

We examined the associations of novel inflammation markers and etiological groups. Novel inflammatory markers were determined using the following method: The AISI was calculated by multiplying the neutrophil count by the monocyte count by the platelet count and then dividing by the lymphocyte count. NLR was calculated as the ratio of neutrophils to lymphocytes. NLPR was calculated as the ratio of neutrophils to the product of lymphocytes and platelets. PLR was calculated as the ratio of platelets to lymphocytes. The MLR is calculated by dividing the number of monocytes by the number of lymphocytes. SII is calculated by multiplying the platelet count by the neutrophil count and dividing by the lymphocyte count. SIRI is calculated by multiplying the neutrophil count by the monocyte count and then dividing by the lymphocyte count.

Statistical Analysis

Descriptive summaries for continuous variables were presented as mean±standard deviation if normally distributed and as median (Q1-Q3) if not normally distributed. Shapiro-Wilk analysis was used for the normality test. CRP measurement under 0.5 mg/l is attributed as a missing value. The Mann-Whitney U test was used to compare ESR values between chronic diseases and gender since the data was not normally distributed. The chi-square test was used to determine the relation between chronic disease groups and etiological groups. The Kruskal-Wallis test was used to compare disease categories with continuous variables that did not have a normal distribution. Post-hoc analysis was performed using the Bonferroni correction. One-way ANOVA is used for normally distributed variables. ROC analysis was performed for inflammatory markers significantly associated with the etiological groups. In the study, p-values less than 0.05 were considered statistically significant. A significance level of $p<0.005$ was used for Bonferroni correction and advocated a letter k, l, and m in Table 1. Statistical analysis was performed with IBM SPSS version 22.

Results

Five hundred ninety-four patients with ESR levels higher than 100 mm/hour were included in the study. Two hundred ninety-one patients who met the inclusion criteria were included in the study. The median age was 58 (18-92), and 94 (32%) of the 291 patients were older than 65. ESR levels were lower in females (113, 106-120) than in males (119, 109-120) ($p=0.015$). The most common comorbidity was hypertension (HT) with 100 patients (34.4%), followed by diabetes mellitus (DM) (26.1%), atherosclerotic cardiovascular disease (ASCVH) (10.7%), chronic pulmonary disease (10%), chronic kidney disease (CKD) (8.2%) (Table 1). There was no significant statistical relationship between ESR levels and chronic diseases.

The distribution of etiological disease categories was as follows: inflammatory (41.9%), infection (35.1%), malignancy (18.2%), renal (3.1%), and others (1.7%). Among the inflammatory diseases, the most common diagnoses were rheumatoid arthritis (RA) (38.5%) and thyroiditis (27.9%) followed by spondyloarthropathies (SPA) (14.8%), others (8.2%) such as sarcoidosis (n: 2) and lupus (n: 2), Familial Mediterranean Fever (FMF) (5.7%) and vasculitis (4.9%). Within infections most prevalent type of infections was pneumonia (36.3%) and urinary tract infection (26.5%) followed by skin infections (15.7%, n:16) such as diabetic foot disease (n: 9) and cellulitis (n: 3), gastrointestinal system infections (GIS) (9.8%), sepsis (3.9%) and others (7.8%) such as HIV (n:3). Malignancy was the third most common diagnostic category with two subdivided groups: hematological (28.3%) and oncological (71.7%). Renal disease was the less frequent cause of the highly elevated ESR. Out of 24 patients with chronic kidney disease, only five had etiology associated with significantly elevated ESR levels without any other relevant cause. Five patients (1.7%) had other detected etiology like primary sclerosing cholangitis and immune thrombocytopenia (Table 2).

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Table 1. Demographic features and laboratory findings of the patient groups

	All groups	Infection	Malignancy	Inflammatory	Renal	Other	p
n	291	102 (35.1%)	53 (18.2%)	122 (41.9%)	9 (3.1%)	5 (1.7%)	
Gender, female	173 (59.4%)	67 (65.7%)	16 (30.2%)	86 (70.5%)	2 (22.2%)	2 (40%)	**<0.001**[a]
Diabetes mellitus	76 (26.1%)	36 (35.3%)	14 (26.4%)	20 (16.4%)	4 (44.4%)	2 (40%)	**0.008**[a]
Hypertension	100 (34.4%)	45 (44.1%)	17 (32.1%)	29 (23.8%)	7 (77.8%)	2 (40%)	**0.001**[a]
Pulmonary disease	29 (10%)	12 (11.8%)	8 (15.1%)	6 (4.9%)	3 (33.3%)	0 (0%)	**0.025**[a]
Heart failure	10 (3.4%)	7 (6.9%)	2 (3.8 %)	1 (0.8%)	0 (0%)	0 (0%)	0.139[a]
ASCVH	31 (10.7)	17 (16.7%)	7 (13.2%)	6 (4.9%)	1 (11.1%)	0 (0%)	**0.045**[a]
Chronic kidney disease	24 (8.2%)	7 (6.9%)	4 (7.5%)	6 (4.9%)	7 (77.8%)	0 (0%)	**<0.001**[a]
Age, year, median (Q1-Q3)	58 (45-68)	62.5 (48.0-73.0)[*k]	65.0 (57.0-73.0)[*l]	50.0 (40.0-59.0)[*k,l]	60.0 (58.0-65.0)	52.0 (41.0-61.0)	**<0.001**[b] **<0.001**[k] **<0.001**[l]
ESR, mm/hour, median (Q1-Q3)	116 (106-120)	115 (106-120)	119 (111-120)	117 (106-120)	111 (105-116)	114 (106-118)	0.158[b]
CRP, mg/l, median (Q1-Q3)	46 (19-93)	48.0 (21.0-141.0)	56.0 (28.0-107.5)	41.0 (15.0-73.0)	56.0 (49.0-86.0)	21.0 (9.0-62.0)	0.036[b]
Albumin, g/l, median (Q1-Q3)	3.7 (3.1-4.03)	3.60 (3.10-4.06)	3.40 (2.70-3.90)[*l]	3.90 (3.50-4.10)[*l]	3.40 (3.19-3.60)	4.00 (3.96-4.00)	**0.005**[b] **0.001**[l]
CAR, median (Q1-Q3)	14.58 (5.5-36.99)	16.47 (5.93-44.75)	17.16 (7.25-40.00)	11.32 (3.85-28.71)	15.28 (14.38-26.96)	7.00 (2.27-15.50)	0.071[b]
Hemoglobin, mean±SD	11.14±1.79	11.3±1.87	10.85±1.71	11.19±1.71	10.19±2.12	11.75±1.48	0.296[b]
Hematocrit, mean±SD	34.78±5.18	35.12±5.47	34.0±5.18	35.04±4.81	31.03±5.91	37.28±3.84	0.175[b]

AISI: aggregate index of systemic inflammation, ASCVH: atherosclerotic cardiovascular disease, CAR: CRP-albumin ratio, CRP: C-reactive protein, NLR: neutrophil-to-lymphocyte ratio, NLPR: neutrophil to lymphocyte platelet ratio, PLR: platelet-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, SII: systemic immune-inflammation index, SIRI: system inflammation response index; a: the chi-square test, b: the Kruskal-Walls Test; k,l,m: letters indicating statistical difference based on post-hoc analysis of Kruskal Walls with Bonferroni correction

Table 1. Demographic features and laboratory findings of the patient groups

	All groups	Infection	Malignancy	Inflammatory	Renal	Other	p
Wbc, median (Q1-Q3)	9.05 (7.38-11.78)	9.48 (7.50-11.86)	9.37 (7.62-12.07)	8.47 (6.98-11.41)	10.51 (10.20-12.46)	8.55 (6.36-10.73)	0.096[b]
Neutrophil, median (Q1-Q3)	6.22 (4.62-8.49)	6.43 (4.86-8.88)	7.08 (5.35-9.01)	5.80 (4.44-7.67)	6.97 (6.54-9.42)	4.24 (4.00-6.56)	0.038[b]
Monocyte, median (Q1-Q3)	0.56 (0.43-0.74)	0.60 (0.44-0.79)	0.64 (0.41-0.83)	0.50 (0.42-0.63)	0.95 (0.72-1.05)	0.51 (0.44-0.78)	0.009[b]
Lymphocyte, median (Q1-Q3)	1.87 (1.37-2.45)	1.77 (1.21-2.45)	1.70 (1.06-2.39)	1.97 (1.59-2.49)	2.01 (1.39-2.41)	2.20 (1.17-3.27)	0.203[b]
Platelet, K/uL, median (Q1-Q3)	336 (263-414)	326 (254-401)	298 (212-381)[*l]	361 (289-433)[*l]	368 (289-372)	358 (315-409)	**0.005[b]** **0.001[l]**
NLR, median (Q1-Q3)	3.24 (2.13-5.32)	3.43 (2.29-5.64)	4.07 (2.64-6.94)[*l]	2.83 (1.90-4.02)[*l]	4.39 (3.20-4.71)	3.38 (1.34-5.58)	**0.004[b]** **0.001[l]**
PLR, median (Q1-Q3)	175.1 (130.4-250.8)	175.3 (139.3-241.9)	174.2 (121.2-278.3)	175.2 (131.3-238.0)	183.1 (164.7-293.1)	172.6 (121.4-336.9)	0.993[b]
MLR, median (Q1-Q3)	0.292 (0.202-0.447)	0.322 (0.236-0.504)[*k]	0.364 (0.207-0.665)[*l]	0.249 (0.181-0.367)[*k,l]	0.373 (0.344-0.539)	0.397 (0.161-0.608)	**<0.001[b]** **<0.001[k]** **0.001[l]**
SII, median (Q1-Q3)	1110.7 (693.6-1848.1)	1173 (717-1975)	1193 (718-2529)	958 (668-1669)	1708 (968-2056)	1129 (514-1825)	0.089[b]
AISI, median (Q1-Q3)	606.5 (323.3-1267.4)	620 (387-1440)	684 (416-1723)	446 (270-977)	1230 (620-1551)	478 (260-1321)	0.024[b]
NLPR, median (Q1-Q3)	0.010 (0.007-0.017)	0.012 (0.007-0.021)[*k]	0.012 (0.009-0.026)[*l]	0.008 (0.005-0.012)[*k,l]	0.012 (0.007-0.015)	0.009 (0.004-0.017)	**<0.001[b]** **0.001[k]** **<0.001[l]**
SIRI, median (Q1-Q3)	1.78 (1.04-4.04)	2.35 (1.11-4.31)[*k]	2.43 (1.37-4.58)[*l]	1.28 (0.90-2.38)[*k,l,m]	3.34 (2.13-4.94)[*m]	1.59 (0.68-3.81)	**<0.001[b]** **0.001[k]** **<0.001[l]** **0.004[m]**

AISI: aggregate index of systemic inflammation, ASCVH: atherosclerotic cardiovascular disease, CAR: CRP-albumin ratio, CRP: C-reactive protein, NLR: neutrophil-to-lymphocyte ratio, NLPR: neutrophil to lymphocyte platelet ratio, PLR: platelet-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, SII: systemic immune-inflammation index, SIRI: system inflammation response index; a: the chi-square test, b: the Kruskal-Walls Test; k,l,m: letters indicating statistical difference based on post-hoc analysis of Kruskal Walls with Bonferroni correction

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Table 2. The etiological causes of elevated ESR levels

Etiology	n	%	Subgroup	n	%
Infection	102	35.1	Pneumonia	37	36.3
			Urinary tract	27	26.5
			Skin	16	15.7
			Gastrointestinal	10	9.8
			Sepsis	4	3.9
			Other	8	7.8
Malignancy	53	18.2	Gastrointestinal	10	18.9
			Multiple myeloma	9	17.0
			Lung	9	17.0
			Lymphoma	5	9.4
			Prostate	4	7.5
			Gynecological	4	7.5
			Renal	3	5.7
			Breast	2	3.8
			Other	7	13.2
Inflammatory	122	41.9	Rheumatoid arthritis	47	38.5
			Thyroiditis	34	27.9
			Spondyloarthropathies	18	14.8
			FMF	7	5.7
			Vasculitis	6	4.9
			Other	10	8.2
Renal	9	3.1	Chronic kidney injury	5	55.6
			Acute kidney injury	4	44.4
Others	5	1.7			
Total	291	100.0			

FMF: familial mediterranean fever

Comparisons of Etiological Diagnoses

The primary etiological groupings were infections, malignancies, and inflammation. Females were more prevalent in the infection and inflammatory groups, while males were more prevalent in the malignancy group ($p<0.001$). Patients in the infection and renal groups had a higher prevalence of diabetes mellitus and hypertension compared to the other groups ($p=0.008$ and $p=0.001$). The distribution of chronic diseases for each group is displayed in Table 1. The patients in the inflammatory group were younger than other groups. ($p<0.001$). Only 20 patients (16.3%) of 122 were older than 65. Albumin levels were lower in the malignancy group than in the inflammatory group ($pl<0.005$). In the Kruskal-Walls test, CRP was statistically different ($p=0.036$), but following post-hoc analysis, no differences were seen within other groups. Neutrophil count ($p=0.038$), monocyte count ($p=0.009$), and AISI ($p=0.0024$) were also significant within groups. CRP-albumin ratio (CAR), hemoglobin levels, hematocrit, white blood cell count, platelet count, PLR, and SII calculations were similar within the groups. Platelet counts of the inflammatory group were higher than other groups ($p=0.005$). In post-hoc analysis, we showed platelet count was significantly lower in the malignancy group than in the inflammatory group ($pl=0.001$). As for the significant differences in inflammation markers, NLR was higher in the malignancy group than in the inflammatory group ($pl=0.001$). MLR, NLPR, and SIRI were lower in the inflammatory group than others ($p<0.001$, $p<0.001$ and $p<0.001$). ROC curves for platelet, albumin, NLR, MLR, NLPR, and SIRI have been calculated to measure their ability to differentiate the inflammatory group from other groups. MLR had the highest area under curve (AUC: 0.655, $p<0.001$), and the cut-off value of MLR which is 0.2775 had 65.3% sensitivity and 65.5% specificity to identify the cases without the inflammatory disease. The cut-off values of other novel inflammatory markers were not reported because of the low sensitivity and specificity Figure 1.

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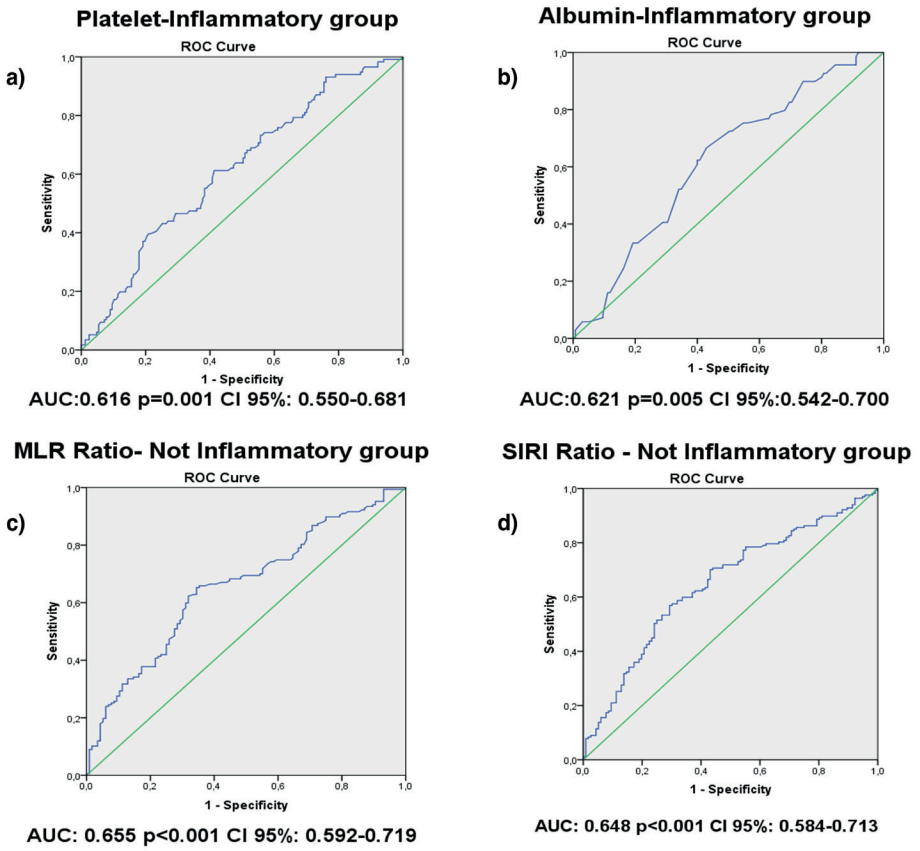

Figure 1. Roc curves; **a.** Platelet-Inflammatory group cut-off value: 337.5 (61.2% Sensitivity and 58.7% Specificity,) **b.** Albumin-Inflammatory group cut-off value: 3.65 (61.2% Sensitivity and 50.7% Specificity) **c.** MLR Ratio- No Inflammatory group cut-off value: 0.2775 (65.3% Sensitivity and 65.5% Specificity) **d.** SIRI Ratio- No Inflammatory group cut-off value: 2.102 (56.9% Sensitivity and 70.7 % Specificity)

Discussion

An elevated erythrocyte sedimentation rate is not always indicative of a disease. Yet the significant increase in ESR to 100 mm/hour requires additional examination for potential disease. Multiple causes may be the cause for elevated ESR levels, which should be evaluated along with symptoms, physical examinations, and further laboratory findings. Identifying prevalent causes can help determine the steps that need to be taken. For this purpose, the etiology of high ESR has been studied in several papers before [1-5,9-11].

A study conducted by Uğuz et al. on the elderly showed infections are the leading cause of highly elevated ESR in geriatric populations [4]. The least frequent etiological cause of high ESR was inflammatory and connective tissue diseases (3.9%). However, in our study, the geriatric population was a minority with 32% of patients, and the inflammatory group patients were significantly younger. In that study, the most frequent diagnoses of malignancy groups were leukemia and multiple myeloma.

Similar to previous reports, in 2020, Aydemir et al.also showed infections are the main cause of extremely elevated ESR [11]. Rheumatological diseases (6.4%) were the fourth etiological cause in contrast to our study. This may be the result of the age of the population, hence in our study inflammatory group patients were mostly under the age of sixty-five, whereas in their study 57.5% of patients were above 65 years old. Also in that study, twenty-five percent of patients were applied to infectious diseases outpatient clinics. In our study, all patients were selected from those who were referred to only internal medicine clinics.

In 2017, Daniels et al. also showed infectious diseases are the most common reason for elevated ESR [5]. Pneumonia was the most common type of infection in their study, confirming the results we obtained. In the study, rheumatoid arthritis was the most frequent diagnosis in the inflammatory/autoimmune group which was also matched with our results. In that study, multiple myeloma was the most frequent cause of highly elevated ESR. Whereas in our study oncological diseases were the most frequent cause.

Erişmiş et al. investigated the causes of elevated ESR levels over 100 mm/hour and how ESR levels correlated with other laboratory tests [10]. Malignancies were the primary diagnosis for all patients and women, while infections were the primary diagnosis in men. They reported hematological malignancies as

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the most common type of malignancy. Also, they reported in the rheumatological group patients were younger, and their platelet counts were higher. These findings were compatible with our results.

In 2020, a study by Kılıç et al. reported malignancies are the most common cause of highly elevated ESR [12]. Thirty-three of 234 patients had lung cancer which was the second cause after metastases. Also, oncological malignancies were higher than hematological malignancies. In that study, 51.2% of patients were women and 59.9% were under 65 years old. In that study, DM and HT were the most frequent accompanying chronic diseases like in our study. In rheumatological diseases, patients were mostly female (71.5%). In our study, we also found 70.5% of patients were female in the inflammatory group.

In a study in 2007, Sarı et al. reported rheumatological diseases (30%) as the leading cause of ESR above 100 mm/hour [13]. They explained this result with their cooperation with the rheumatology department in their inpatient clinic during that period. In that study, the mean age of patients was 49.1±22.9 years. In our study, the median age was 58 years, but the population was relatively younger than in other studies. Their population was also younger than other studies conducted on adults.

There are several studies in the literature about the correlation between ESR and CRP [7,8]. In our study we did not find any significant difference in CRP between groups. In literature, some studies have reported relations between inflammatory diseases with novel inflammation markers. In a study Yunyun et al. conducted, 1499 RA patients and 366 healthy individuals were compared. They reported NLR and SIRI significantly increased in RA patients, and ROC curves of SIRI and NLR could differentiate RA patients from healthy controls. In addition, they stated that the levels of SIRI increased in rheumatoid arthritis patients who also had malignancy. Within our research, we observed that the inflammatory group had lower levels of SIRI and NLR. However, we conducted an analysis between the group with inflammation and other groups that had different diseases. In our investigation, we observed that SIRI was similarly elevated in the cancer group, which is consistent with the results documented by the researchers [14]. Erge et al. reported that PLR was higher in autoimmune thyroiditis than in healthy controls in their study. They explained their finding with the stimulation of bone marrow, which results in a decreasing number of lymphocytes while platelets are produced. In our research, PLR was similar in all groups, whereas platelet counts were significantly higher in the inflammatory group than in the cancer group. Bone marrow depression in cancer patients can lead to a decreasing number of platelets, lymphocytes, and PLR ratio [15]. Fan et al. also showed increased platelet counts in subacute thyroiditis patients [16].

The neutrophil-to-lymphocyte ratio is a widely used immune marker. The studies have shown its relation to inflammation, infection, malignancy, and stress. A typical range for NLR is between 1.0-2.0, and higher than 3.0 or lower than 0.7 is often related to pathological conditions. Also, 2.3-3.0 is accepted as a gray zone. In our study, the median NLR for all patients was 3.24 [17]. This was an expected result as all patients had possible diseases with an extremely high ESR. Unexpectedly patients in the inflammatory group had the lowest NLR with a value of 2.83, which is considered to be within the gray zone. A comprehensive analysis might be undertaken to compare the inflammatory group with undiagnosed individuals who have high ESR with the aim of developing a complete understanding.

In our study, one of the distinctive results of the inflammation group was low MLR. There are some studies on the normal range of MLR and cut-off values [18]. One of the studies reported that the mean MLR of patients with bladder cancer was higher than that of patients without bladder cancer. They reported an MLR of 0.41±0.11 for bladder cancer patients and 0.38±0.43 for patients without bladder cancer [19]. In our study, the MLR of cancer patients was 0.364 (0.207-0.665), which is significantly higher than inflammation group patients with MLR of 0.249 (0.181-0.367).

There are also several studies with inflammation markers and inflammatory diseases such as spondyloarthropathies [20], inflammatory bowel diseases [21], and Behcet's disease [22]. These studies show the relationship between inflammatory markers with the disease itself or disease activity. In our study, we used these markers to understand different types of diseases in a population with increased ESR.

In our clinic, ESR is a commonly used laboratory test to determine to investigate further malignancies, not only in hematological but also for oncological malignancies. Also in our clinic, there was not a chemotherapy center for hematological malignancies. Therefore, patients with abnormal blood cell counts were often referred to other medical centers in that period. This may be the reason for fewer hematological malignancies than other studies. We found significant differences in inflammatory markers. However, AUCs were not optimal for selecting each case.

Study Limitations and Strength

The strength of the study is that it is the first study to evaluate the use of novel inflammatory markers to differentiate the etiology of high ESR with ROC curves. Our study has some limitations. This is a single-center and retrospective study that investigates the patients with high ESR levels. The study was conducted on patients in internal medicine clinics. For further research, expanding the branches of medicine can provide better insight into the etiology of high sedimentation rates.

Conclusion

This study presents the causes of significantly increased ESR and its correlation with new inflammatory markers. We found significant differences within groups, particularly in the inflammatory group. We found a positive relationship between the inflammatory group platelet count, and albumin. We also found a negative correlation between the inflammatory group and NLR,

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MLR, NLPR, and SIRI. We believe novel inflammatory markers that are inexpensive and simple can be used for etiological investigation of high erythrocyte sedimentation rate. These data can assist clinicians in identifying underlying etiology and prevent unnecessary distribution of resources.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical Approval
For this study, approval was obtained from the Sancaktepe Şehit Prof. Dr. Ilhan Varank Training and Research Hospital ethical committee with decision number 2023/140.

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