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Investigation of Diagnosis in Patients with Higher than 100 mm/Hour Erythrocyte Sedimentation Rate and Differences of Genders, Age Groups, Co-morbidities and Mortality Rates

Eritrosit Sedimantasyon Hızı 100 mm/h Yüksek Hastaların Tanılarının Araştırılması ve Cinsiyet, Yaş Grupları, Ko-morbidite ve Mortalite Oranlarındaki Farklılıklar

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ABSTRACT Objective: We aimed to explain the differences of genders, age groups, co-morbidities and mortality rates in patients with erythrocyte sedimentation rate (ESR) value above 100 mm/hour. **Material and Methods:** The retrospective study includes adults aged 18 and over who had an ESR above 100 mm/hour. Demographic and co-morbidity characteristics of all patients were recorded. Patients were stratified according to these 5 diagnostic categories: infectious diseases, hematological/oncologic diseases, renal diseases, rheumatic diseases and others. **Results:** Data of 746 patients who met the inclusion criteria out of 1581168 patients were collected. Most of patients with an ESR above 100 mm/hour were in hematological/oncologic patients category (234 patients, 31.4%). Of the patients whose ESR values were above 100 mm/hour, 32.2%, 40.1% and 52.9% died in 6 months, 1 years and 4 years, respectively. The most common co-morbid diseases of all patients according to their medical history were diabetes mellitus in 149 patients, and malignity in 144 patients. While rheumatic diseases were more common in females as compared to males (p<0.001), hematological/oncologic diseases were more common in males (p=0.009). While rheumatic diseases were more common in non-elderly patients as compared to the elderly ones, undiagnosed diseases were more common in elderly than non-elderly (respectively; p=0.003, p=0.031). **Conclusion:** It may be thought that very high ESR values contribute to high mortality rate. In addition, this study, in which diagnostic differences of age, gender and co-morbidity, should be supported by further studies, considering other conditions that may be related.

Keywords: Blood sedimentation; co-morbidity; elderly; gender; mortality

ÖZET Amaç: Eritrosit sedimantasyon hızı (ESR) 100 mm/saatin üzerinde olan hastalarda cinsiyet, yaş grupları, ko-morbidite ve mortalite oranlarındaki farklılıkları açıklamayı amaçladık. **Gereç ve Yöntemler:** ESR değeri 100 mm/saat üzerinde olan tüm 18 yaş üstü hastalar retrospektif olarak çalışmaya alındı. Hastaların demografik ve ko-morbid özellikleri kaydedildi. Hastalar 5 tanı kategorisine göre sınıflandırıldı: Enfeksiyon hastalıkları, hematolojik/onkolojik hastalıklar, böbrek hastalıkları, romatolojik hastalıklar ve diğerleri. **Bulgular:** Taranan toplam 1581168 hastadan dahil edilme kriterlerine uyan 746 kişi alındı. ESR değeri 100 mm/saat üzerinde olan hastaların çoğunluğu hematolojik/onkolojik hasta kategorisinde idi (234 hasta, %31,4). ESR değeri 100 mm/saat ve üzeri hastaların %32,2'si 6 ay içinde, %40,1'i 1 yıl içinde, %52,9'u 4 yıl içinde hayatını kaybettiler. Tüm hastaların özgeçmişlerine göre en yaygın ko-morbid hastalıkları diabetes mellitus (149 hasta) ve malignite (144 hasta) idi. Romatizmal hastalıklar erkeklerle karşılaştırıldığında kadınlarda daha yaygın (p<0,001) iken, hematolojik/onkolojik hastalıklar ise kadınlara kıyasla erkeklerde daha yaygındı (p=0,009). Romatolojik hastalıklar ise yaşlılarla karşılaştırıldığında yaşlı olmayanlarda daha yaygın iken, tanı konulamamış hastalıklar ise yaşlı olmayanlara kıyasla yaşlılarda daha yaygın idi (sırasıyla; p=0,003, p=0,031). **Sonuç:** Çok yüksek ESR değerlerinin, yüksek oranda mortalite hızına katkıda bulunduğu düşünülmektedir. Ayrıca tanısal olarak yaş, cinsiyet ve ko-morbidite farklılıklarının ortaya konulduğu bu çalışmanın ilişkili olabileceği diğer durumlar dikkate alınırak, daha ileri çalışmalarla desteklenmesi gerekir.

Anahtar Kelimeler: Kan sedimantasyonu; ko-morbidite; yaşlı; cinsiyet; mortalite

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Infections, immunological processes, tissue damage and inflammatory episodes cause a systemic response in the organism within hours or days. This state is called acute phase response and its products are called acute phase reactants. Erythrocyte sedimentation rate (ESR) is a commonly used test to evaluate acute phase response. ESR starts to increase 24 hours after the inflammation and its fall back to baseline levels may last up to a month. Main principle of the test is the fall of erythrocytes in a well-mixed venous blood with an anticoagulant agent in a vertical tube due to gravity because erythrocytes have more specific weight comparing to plasma.[1]

Very high ESR values have low false positivity for presence of a serious illness. In many studies, it is reported that infectious states, collagen vascular diseases, metastatic malign tumors and renal diseases might cause very high ESR values.[2]

We aimed to explain the differences of genders, age groups, co-morbidities and mortality rates in patients with erythrocyte sedimentation rate (ESR) value above 100 mm/hour.

MATERIAL AND METHODS

Population of the study includes patients who had an ESR above 100 mm/hour in their routine medical workup and treatment during their first application or control visits in outpatient or inpatient clinics of a tertiary university medical hospitals for 24 months between 01 January 2013 and 03 December 2014. Patient charts in the archives were evaluated retrospectively according to time of application and patient protocol number. The study included all patients aged 18 and over who had an ESR above 100 mm/hour. Patients who had multiple entries were included only when they had an ESR value above 100 mm/hour.

Demographic and co-morbidity characteristics of all patients included in the study were recorded according to prepared patent chart. In line with the data acquired from the charts, patients were stratified with the most probable diagnosis into categories of infectious diseases, hematological/oncologic diseases, renal diseases, rheumatic diseases and others. The "others" group was for patients without a diagnosis. Diagnosis, co-morbidity status, mortality rates, genders, elderly and non-ederly distributions of all these groups were analyzed.

ESR MEASUREMENT

ESR measurements were performed with TEST1 TH device (Alifax, Italy) in Erciyes University Medical Faculty Central Laboratory. System is closed loop, safe and controlled. Blood tubes with EDTA can be directly analyzed without requiring a pretreatment. In our hospital, bloods were collected in a purple-topped vial with 5.4 mg (tripotassium) K3EDTA in an amount of 3 cc. The test is based on photometrical capillary flow kinetic analysis. The system performs approximately 1000 readings in 20 seconds after 3 minutes of mixing by using infrared ray micro-photometry with a light wavelength of 950 nm. 60 samples can be processed at the same time and it can process 180 samples in an hour.

STATISTICAL ANALYSIS

Data were analyzed with Statistical Packages of Social Sciences (SPSS 22.0 for Windows, version 22.0) software. Frequencies were expressed in percentage (%). Parametric variables were presented as means and standard deviations, non-parametric variables were presented as medians and interquartile ranges (25^{th}-75^{th} percentiles). Shapiro-Wilks test and histograms analyses were used to determine whether continuous variables were normally distributed. Two independent groups of parametric variables were compared using Student t test. Data were analyzed using Chi-square test. The confidence interval (CI) was 95% for analysis and $p<0.05$ was accepted significant statistically.

ETHICAL CONCERNS

This trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. Local ethics committee approval was received for this study from Erciyes University Ethics Committee in 05.02.2016 with issue number of 2016/82.

RESULTS

A total of 746 patients were identified according to inclusion criteria. Of these patients, 382 were female

(51.2%) and 364 (48.8%) were male. Mean age of female patients was 58.11±16.30 while it was 60.26±14.64 for male patients.

Data of 746 patients who met the inclusion criteria of the study were acquired among 1581168 patients from outpatient and inpatient clinics of the hospital. Of these 746 patients, mean ESR value was 110.64±6.9 while it was 110.48±6.85 in female patients and 110.80±7.02 in male patients. There was no statistically significant differences when ESR values were compared (p=0.520).

Most common symptoms of the patients during their first presentation were arthralgia (11.4%), shortness of breath (11.0%), stomach ache (10.1%), asthenia (9.1%), wound-discharge (8.4%) and fever (7.0%). Of the patients, 16.8% were applying for the follow up of their chronic diseases.

A total of 447 (59.9%) patients were aged under 65 while 299 (40.1%) were over 65. In the group of patients aged over 65, hypertension, chronic renal failure, coronary artery disease and cerebrovascular disease were significantly higher (respectively; p=0.001, p=0.009, p<0.001, p=0.008). Most common co-morbid diseases of all patients according to their medical background were as follows: diabetes mellitus in 149 patients, malignity in 144 patients, hypertension in 133 patients, chronic kidney failure in 91 patients, coronary artery disease in 57 patients, chronic obstructive pulmonary disease (COPD) in 35 patients and cerebrovascular disease in 15 patients. Percentage distribution by age of these patients is given in Table 1.

When diagnostic categories of patients were compared with gender, rheumatic diseases were more common in females as compared to males (p<0.001). Hematological/oncologic diseases were more common in males than females (p=0.009). Infections, renal and other diseases were observed at an equal rate (Table 2).

Diagnostic categories were also compared with age group in patients (Table 3). While rheumatic diseases were more common in non-elderly patients as compared to elderly ones, undiagnosed diseases were more common in the elderly than non-elderly (respectively; p=0.003, p=0.031).

TABLE 1: Distribution of patients over and under age of 65 according to co-morbidity.

Co-morbid diseases	< 65 years n (%)	≥ 65 years n (%)	p value
Diabetes mellitus	84 (56.4)	65 (43.6)	0.320
Malignity	81 (56.3)	63 (43.8)	0.310
Hypertension	63 (47.4)	70 (52.6)	0.001
Chronic renal failure	43 (47.3)	48 (52.7)	0.009
Coronary artery disease	20 (35.1)	37 (64.9)	<0.001
Chronic obstructive pulmonary disease	18 (51.4)	17 (48.6)	0.290
Cerebrovascular disease	4 (26.7)	11 (73.3)	0.008

Frequencies were expressed in percentage (%).
(p<0.05 considered statistically significant)

TABLE 2: Patient numbers of diagnostic categories according to genders.

Diagnostic categories	Female, n (%)	Male, n (%)	p value
Rheumatic diseases	68 (17.8)	27 (7.4)	<0.001
Infectious diseases	111 (29.1)	111 (30.5)	0.689
Hematological/oncologic diseases	103 (26.9)	131 (35.7)	0.009
Renal diseases	24 (6.3)	23 (6.3)	0.999
Others (undiagnosed)	76 (19.9)	72 (19.8)	0.999
Total	382	364	

Frequencies were expressed in percentage (%).
(p<0.05 considered statistically significant).

TABLE 3: Patient numbers of diagnostic categories according to age groups.

Diagnostic categories	< 65 years, n (%)	≥65 years, n (%)	p value
Rheumatic diseases	70 (15.7)	25 (8.4)	0.003
Infectious diseases	129 (28.9)	93 (31.1)	0.514
Hematological/oncologic diseases	148 (33.1)	86 (28.8)	0.227
Renal diseases	23 (5.2)	24 (8.0)	0.125
Others (undiagnosed)	77 (17.2)	71 (23.8)	0.031
Total	447	299	

Frequencies were expressed in percentage (%).
(p<0.05 considered statistically significant)

In total, 395 patients died within four years. Of these 395 patients, 235 were male and 160 were female. The group with most deaths was hematologi-

cal/oncologic diseases (n=170). From the moment of an ESR value above 100 mm/hour was identified, deaths occurred increasingly according to patient-time curve with a ratio of 32.2% in six months, 40.1% in one year and 52.9% in four years (Figure 1).

The most patients with an ESR above 100 mm/hour were in hematological/oncologic patients category (234 patients, 31.4%). This group consisted 88 patients (11.8%) with hematological diseases and 146 patients (19.6%) with oncologic diseases. The second most common category with an ESR above 100 mm/hour was infectious diseases (222 patients, 29.8%). Most common cause of infectious diseases was pneumonia in 33 patients (14.9%), followed by diabetic foot in 24 patients (10.8%). All diagnostic categorical distribution of patient groups is given in Figure 2.

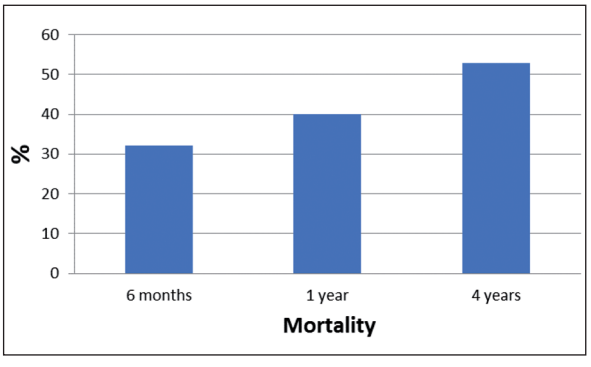

FIGURE 1: Mortality rates per year.

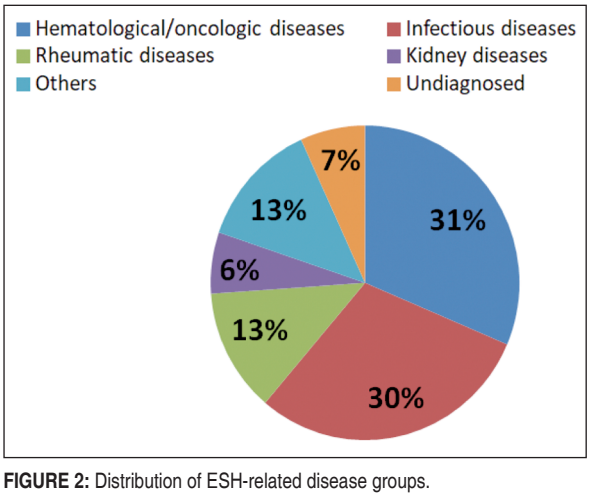

FIGURE 2: Distribution of ESH-related disease groups.

TABLE 4: Number of patients with hematological/oncologic patients according to their diagnosis.

Diagnostic distribution	Female, n	Male, n	Total, n
All diseases	103	131	234
Metastases	16	24	40
Malign neoplasm of lungs	4	29	33
Multiple myeloma	14	16	30
Hodgkin lymphoma	6	6	12
Anemia	10	1	11
Malign neoplasm of biliary tract	8	3	11
Malign neoplasm of pancreas	3	6	9
Malign neoplasm of colon	7	2	9
Myelodysplastic syndrome	3	5	8
Renal cell carcinoma	2	6	8
Acute myeloid leukemia	5	2	7
Gastric malign neoplasm	3	3	6
Diffuse large B cell lymphoma	2	3	5
Non-Hodgkin lymphoma	1	3	4
Malign neoplasm of ovaries	4	0	4
Pleural mesothelioma	0	4	4
Acute lymphoblastic leukemia	2	1	3
Malign neoplasm of breast	2	1	3
Malign neoplasm of bladder	1	2	3
Waldenström macroglobulinemia	1	1	2
Malign neoplasm of duodenum	2	0	2
Hepatocellular carcinoma	0	2	2
Thrombotic thrombocytopenic purpura	1	0	1
Castleman syndrome	1	0	1
Granulocytic sarcoma	1	0	1
Glioblastoma multiforme	1	0	1
Neuroendocrine tumor	1	0	1
Squamous cell carcinoma	1	0	1
Malignant neoplasm of endometrium	1	0	1
Maltoma	0	1	1
Autoimmune hemolytic anemia	0	1	1
Erdheimchester disease	0	1	1
Graft-versus-host disease	0	1	1
Mediastinal malign neoplasm	0	1	1
Malign neoplasm of salivary gland	0	1	1
Leiomyosarcoma	0	1	1
Atrial leiomyosarcoma	0	1	1
Fibrosarcoma	0	1	1
Malign melanoma	0	1	1
Thymus malign neoplasm	0	1	1

Among hematological/oncologic diseases, an ESR value above 100 mm/hour was the most common in metastases, followed by lung cancer and multiple myeloma (Table 4).

DISCUSSION

ESR level, which is used for public screening, is reported significantly higher in females than males in many studies.[3-5] This study conducted among patients with an ESR value above 100 mm/hour, is valuable because it obtains results after excluding healthy individuals. Even though females tend to have higher levels of ESR in general population, one should keep in mind that there might not be a gender variability in case of a pathological status.

In the study of Cankurtaran et al., 80 of 130 patients (57.6%) aged between 16-89 who were followed for two years, had increased ESR levels.[6] In their study, there was no statistically significant difference between elder and non-elder patients when compared for underlying probable cause of ESR increase. When co-morbidities in patient medical backgrounds were examined, ESR of elderly patients was statistically significantly increased in all diseases except COPD. In our study, in a similar manner, ESR values showed no statistically significant difference when compared between elderly and non-elderly groups for underlying cause of ESR increase. Also, coexisting comorbid diseases were mostly in line with the literature. In our study; rheumatologic diseases were more common in non-elderly patients, whereas in elderly patients, undiagnosed diseases were more frequent. This may be due to the fact that the elderly have died before they can be diagnosed.

Although it is a known fact that ESR increases with increasing age, it should be taken into account that it might not show age variability in case of a pathological situation. Obtaining results in line with the literature, also gives rise to thought of contribution of comorbid diseases to increased ESR levels. Both two large studies conducted for very high levels of ESR in childhood, reported infectious diseases as the most common cause, while malignity was the third common cause.[7,8] Hematological/oncologic diseases being the most common cause in our study can be explained with increased incidence of cancer cases among adults as compared to pediatric patients in the community.

A study of Haque et al. which was conducted between January 2004 and March 2004 and published in 2007, included 100 patients who had an ESR value above 100 mm/hour.[9] Of the patients, consisting 56% males and 44% males, the most common admission complaints were fever and asthenia. Also patients were stratified as follows: 41% hematological diseases, 36% infectious diseases, 17% rheumatic diseases and others. Our study which was much more extensive in terms of time and patient count, had similar frequencies with this study. Even though fever and asthenia are among common complaints in our study, the most common was arthralgia.

In the 1986 study of Fincher et al. which consisted 1006 patients who had ESR ≥100 mm/hour, most common causes of ESR, according to the order of frequency were; infectious diseases (33%), malign diseases (17%), kidney diseases (17%) and inflammatory diseases (14%).[10] In a large study conducted in Internal Medicine Department of GATA Hospital, Turkey, patients who were treated between 1992 and 2005 were retrospectively scanned and this study aimed to find diagnosis and ratios of diseases in 797 patients who had a level of ESR ≥ 100 mm/hour. In that study of Sari et al., infection-induced pathology was identified in 44.6% patients, while hematological/oncologic malignities were the second most common cause with 38.7%.[11] In that study, when distribution according to diagnostic criteria was analyzed, the highest rate was rheumatic diseases (n=239, 22.5%), followed by hematological/oncologic diseases (n=165, 20.7%). In a study of Yousuf et al. conducted in 2010, main causes of ESR increase above 100 were researched in 508 patients. Infectious diseases were the most common among diagnostic groups with 38.6% ratio, autoimmune diseases were second most common with the ratio of 15.9% and malignities were the third most common with the ratio of 15.4%.[12] Difference of most common cause being malignities in our study indicates to what extent frequency of malign diseases increased in time. It also suggests an increase in ability to diagnose malign diseases in line with advancing technology and growing opportunities. This situation also may differ due to differences in race and geographical location.

In a study of Jin go et al. conducted in 2015, contribution of ESR value to mortality rates in dermatomyositis patients were researched; and patients with

a baseline level of ESR ≥ 30 had significantly higher rates of mortality as compared to the patients with a baseline level of ESR < 30.[13] Also patients who had persistent increase of ESR level in spite of immunosuppressive treatment were associated with higher rate of mortality. Patients with increased ESR levels were evaluated for mortality rates based on time. Accordingly, an increase was observed in mortality-time curve of patients. Especially, mortality rates were 32.2% in the first six months. An increase of 0.05-8.0% was observed between six months and one year and for every year afterwards. 235 male patients died during the period of the study, while 160 female patients died in the same period. Most deaths occurred in hematological/oncologic patients (n=170). Diseases that lead to an ESR level above 100 mm/hour had more contribution to mortality comparing to other diseases. The cause of this might be that diseases which cause an increase of ESR level above 100 mm/hour are mostly severe diseases (malignities, rheumatic diseases with multi-system involvement and severe infectious diseases). Main causes of mortality in patients is not clear whether it is due to primary disease that increases ESR or co-existing co-morbidity. Whatever the cause is, diseases associated with high levels of ESR are related with mortality and this increase shows a correlation with time. Also, one should keep in mind that increasing ESR levels in patients followed with a malignity, might point out the onset of metastatic disease.

There are some limitations in our study. First, values of ESR level <100 mm/h are not included in the study. However, our study was planned to evaluate the diagnosis and mortality points of patients over 100 mm/h. Second, no direct relation can be established that the high ESR level causes an increase in mortality. However, ESR values over 100 mm/h may indicate a serious disease, and the diagnostic attention and fatal processes of these diseases are emphasized in our study. Third, even if the main diagnoses of the patients are known, the hospital data records are insufficient regarding the diagnosis that causes death, therefore the causes of mortality could not be provided.

CONCLUSION

It may be thought that very high ESR values contribute to high mortality rate. In addition, this study, in which diagnostic differences of age, gender and co-morbidity, should be supported by further studies, considering other conditions that may be related.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mesut Kılıç, Bülent Eser;* ***Design:*** *Mesut Kılıç, Ulaş Serkan Topaloğlu;* ***Control/Supervision:*** *Bülent Eser;* ***Data Collection and/or Processing:*** *Mesut Kılıç, Duygu Kadagöl Kılıç;* ***Analysis and/or Interpretation:*** *Bülent Eser, Ulaş Serkan Topaloğlu;* ***Literature Review:*** *Mesut Kılıç, Ulaş Serkan Topaloğlu;* ***Writing the Article:*** *Mesut Kılıç, Ulaş Serkan Topaloğlu;* ***Critical Review:*** *Bülent Eser, Ulaş Serkan Topaloğlu;* ***References and Fundings:*** *Mesut Kılıç, Duygu Kadagöl Kılıç;* ***Materials:*** *Mesut Kılıç, Duygu Kadagöl Kılıç.*

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