IS THE NEUTROPHIL-TO-LYMPHOCYTE RATIO DIFFERENT IN SARCOIDOSIS AND INTERSTITIAL LUNG DISEASES?

SARKOİDOZ VE İNTERSTİSİYEL AKCİĞER HASTALIKLARINDA NÖTROFİL LENFOSİT ORANI FARKLI MIDIR?

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Keywords: Neutrophil lymphocyte ratio, sarcoidosis, interstitial lung disease
Anahtar sözcükler: Nötrofil lenfosit oranı, sarkoidoz, interstisiyel akciğer hastalığı

Geliş tarihi: 27 / 07 / 2017 Kabul tarihi: 16 / 08 / 2017

SUMMARY

Introduction: *In the last few years the neutrophil-to-lymphocyte rate (NLR) is gaining attention as a new inflammatory marker. The aim of our study was to investigate the NLR values of sarcoidosis and interstitial lung disease patients at the first admission to the hospital.*

Material-method: *The study consists of patients diagnosed with the ICD codes D86 (sarcoidosis), J84 (interstitiel lung disease) between 2008 and 2014 identified using the hospital automation system.The age, ender,hematologic parameters, C-reaktive protein (CRP), sedimentation,angiotensin converting enzyme (ACE) levels on first admission to hospital were analyzed and the NLR values were calculated. Both disease groups were compared according to the present parameters.*

Results: *In our study 4704 patients diagnosed with the ICD codes J84 (interstitial lung disease) and D86 (sarcoidosis) in the hospital automation system were evaluated and 1039 patients that met*

ÖZ

Giriş: *Son yıllarda nötrofil lenfosit oranı (NLO) yeni bir inflamatuat marker olarak önem kazanmaktadır. Literatürde sarkoidoz, tüberküloz ve interstisiyel akciğer hastalıkları ile NLO arasındaki ilişki çok az çalışmada yer almıştır. Bu çalışmada amacımız sarkoidoz ve interstisiyel akciğer hastalığı tanısı almış hastalarda ilk başvuru sırasında NLO arasında fark olup olmadığını değerlendirmektir.*

Gereç ve Yöntem: *Hastanemiz otomasyon sisteminde 2008-2014 yılları arasında ICD kodlama sisteminden D86(sarkoidoz) ve J84 (Interstisiyel akciğer hastalığı) ve alt kodları girilen hastalar taramaya alındı. Bu hastaların dosyaları incelenerek tanısı kesin olmayanlar çalışma dışı bırakıldı. Çalışmaya dahil edilen hastaların ilk başvuru sırasındaki yaş, cinsiyet, hematolojik parametreler, C- reaktif protein (CRP), sedimentasyon, Angiyotensin dönüştürücü enzim (ACE) ve NLO değerleri kaydedildi ve heriki hastalık grubu bu parametreler açısından karşılaştırıldı.*

the inclusion criteria were included in the study. The difference in age and gender between both groups was statistically significant. The white blood cell, neutrophil, monocyte and lymphocyte count was higher in the interstitial lung disease group than the sarcoidosis group and the difference was significant statistically (p<0.001). On the other hand the NLR was calculated as 2.37±3.1 in the sarcoidosis group and as 2.45±4.4 in the interstitial group however this difference was not statistically significant (p=0.53).

Discussion: *In our study it is difficult to say that the NLR values of patients at hospital admittance benefit the doctor in differentiating sarcoidosis and interstitial lung diseases.We recommend planning future studies to investigate the value of NLR in patient monitoring rather than differential diagnosis.*

Bulgular: *Çalışmada hastane otomasyon sisteminde sarkoidoz ve interstisiyel akciğer hastalığı olarak tanı almış ve International Classification of Disease diagnostic code (ICD) sistemine göre D86 ve J84 olarak kodlanmış 4709 hasta taramaya alındı. Dahil edilme kriterlerine uyan 1039 hasta analiz edildi. Sarkoidoz grubunda yaş ortalaması 49±14 olup % 67'si kadındı. İnterstisiyel akciğer hastalıkları grubunda ortalama yaş 60±17 olup % 57'si kadın idi. Gruplar arasında yaş ve cinsiyet bakımından istatistiksel olarak anlamlı fark vardı. İnterstisiyel akciğer hastalığı grubunda beyaz küre sayısı, nötrofil, monosit ve lenfosit sayısı anlamlı olarak yüksek saptandı (p<0.001). Öte yandan sarkoidoz grubunda NLO 2.37±3.1,interstisiyel akciğer hastalığı grubunda ise 2.45±4.4 olarak hesaplandı ve aradaki fark istatistiksel olarak anlamlı değildi (p=0.53).*

Tartışma: *Çalışmamızda sarkoidoz ve interstisiyel hastalık grubunda ilk başvuruda NLO değerleri arasında fark saptanmamıştır ve ilk başvuruda ayırıcı tanıda yardımcı bir parametre olduğu söylenemez. İleride planlanacak çalışmalarda, NLO değerinin ayırıcı tanıdan ziyade bu hastalık gruplarının takibinde kullanılması önerilebilir.*

INTRODUCTION

In the last few years the neutrophil-to-lymphocyte rate is gaining attention as a new inflammatory marker (1-4). There are studies that have shown the presence of a relationship between high NLR values and poor prognosis in acute coronary syndromes and invasive coronary procedures (3-5). Some studies have also shown a relationship between the prognosis ofcolorectal cancer, mesotheliomas and lung cancers (6-9).

The relationship of NLR and lung cancer is one of the fields of lung diseases that has been researched more often. There are very few studies researching NLR values in tuberculosis, sarcoidosis and interstitial lung diseases (6,10).

This study was planned in a tertiary Chest Diseases Research and Education hospital with approximately 1000 patient beds and aimed to investigate the NLR values of sarcoidosis and interstitial lung disease patients and the differences between them.

MATERIAL AND METHODS

This study was designed as a retrospective cohort study and was conducted in a tertiary teaching hospital with a high patient bed capacity. The study was approved by the local ethics committee of the hospital in consistence with the Declaration of Helsinki. All data were collected retrospectively from the hospital data base. Due to the retrospective nature of the study design, informed consent was not obtained.

Patients

Study population: The population consists of patients diagnosed with the International

Classification of Disease diagnostic code (ICD) codes D86, J84 and the sub codes of these groups between 1 January 2008 and 31 December 2014 identified using the hospital automation system. The data of these patients on first admission to the hospital,recorded in the hospital automation system were analyzed and patients that met the inclusion criteria were included in the study.

Definitions of ICD codes of sarcoidosis

The definitions of the ICD codes D86 and sub-codes in our hospital automation system:

D86.0 Lung sarcoidosis; histopathologically confirmed diagnosis of sarcoidosis with parenchymal lung involvement

D86.1 Lymph node sarcoidosis: histopathologically confirmed diagnosis of sarcoidosis with mediastinal LAPs

D86.2 Lung sarcoidosis, with lymph node sarcoidosis: histopathologically confirmed diagnosis of sarcoidosis with mediastinal lymph node and lung parenchyma involvement

D86.3 Skin sarcoidosis, histopathologically confirmed

D86.8 Sarcoidosis, of other and combined areas; histopathologically confirmed diagnosis of sarcoidosis in extrapulmonary organs.

D86.9 Sarcoidosis unspecified; patients tested after suspicion of sarcoidosis but not proven histopathologically

Definitions of ICD codes of interstitial lung diseases:

J84.0 Alveolar and parieto-alveolar conditions

J84.1 Interstitial lung disease, other, with fibrosis

J84.2 Interstitial lung diseases, other

J84.8 Interstitial lung diseases, other, unspecified

J84.9 Interstitial lung disease, unspecified

NLR: It is obtained by dividing the absolute neutrophil count by the absolute lymphocyte count in the hemogram results.

Data

Electronic data were collected from the hospital data base. After identifying patients diagnosed with the ICD codes D86 and J84 within the specified time frame from the hospital records, patients coded as D86.9 (sarcoidosis unspecified) and J84.9 (interstitial lung disease unspecified)and that did not have hemogram records were excluded from the study (figure 1 flowchart). Patients with specified interstitial lung disease, sarcoidosis and hemogram records were included in the study.

The age, gender, hematologic parameters (hemoglobin, hematocrit, platelets, CRP, sedimentation, angiotensin converting enzyme (ACE) levels on admission were analyzed and the NLR values were calculated from the hemogram parameters in all patients that met the inclusion criteria. The NLR value was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Spirometry values and radiological data of patients could not be recorded because of the lack of electronically available data. Both disease groups were compared according to the present parameters.

Statistical Analysis

The definitive statistical data are expressed as frequency, percentage, mean and standard deviation (SD). In the comparison of the categorical variables we used the chi square test and for the comparison of continuous variables we used the parametric (the t-test) and the non-parametric (Mann-Whitney U) tests in both groups. The p value <0.05 was considered significant for statistical analyzes.

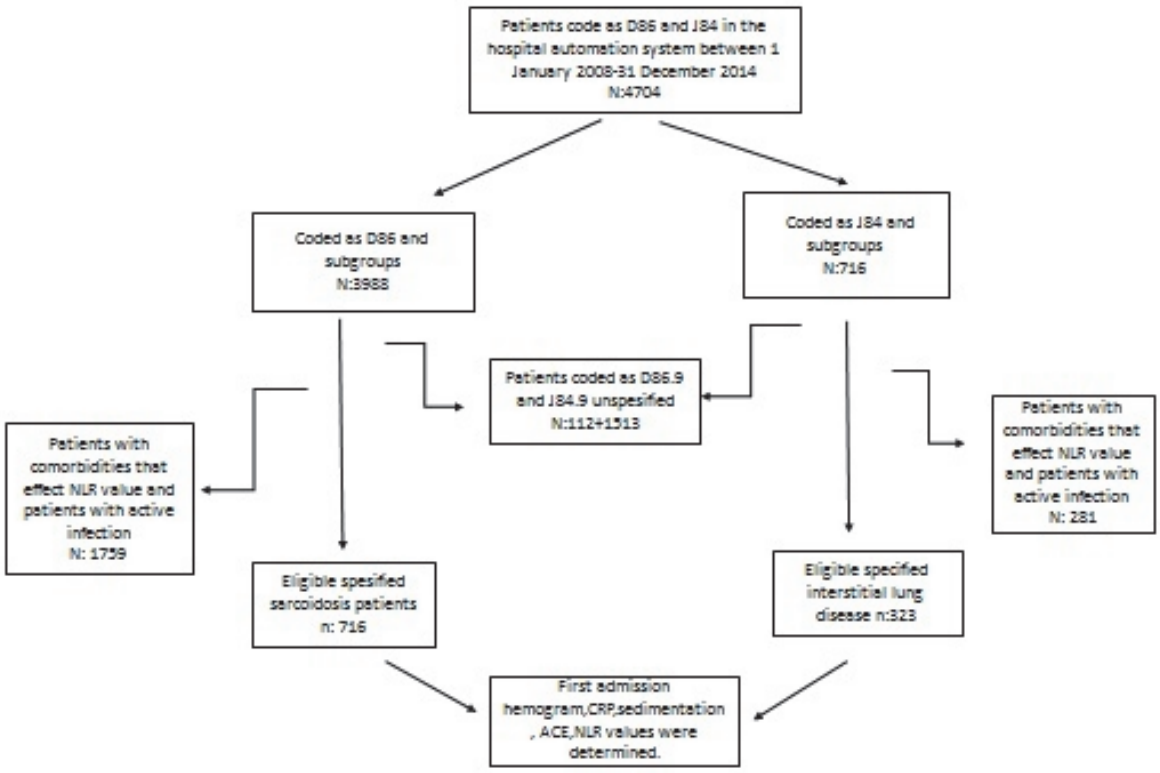

Figure 1. flowchart

RESULTS

For the study 4704 patients diagnosed with the ICD codes J84 and D86 in the hospital automation system were evaluated and 1039 patients that met the inclusion criteria were included in the study.

The mean age of the sarcoidosis patients included in the study was 49 ± 14 years and 67% of the patients were female. In the interstitial patient group the mean age was higher and was calculated as 60 ± 17 years and 57% of the patients were female. The difference in mean age and gender distribution between both groups was statistically significant (Table 1).

When the hemogram parameters of the groups were compared it was seen that the white cell neutrophil, monocyte and lymphocyte count was higher in the interstitial lung disease group than the sarcoidosis group and the difference was highly significant statistically (Table 1, $p<0.001$). The hemogram parameters hemoglobin, hematocrit, MCV, platelet, MPV were similar in both groups (Table 1).

On the other hand the NLR was calculated as 2.4 ± 3.1 in the sarcoidosis group and as 2.5 ± 4.4 in the interstitial lung disease group however this difference was not statistically significant (Table 2, $p=0.53$).

Table 1. The comparison of age, gender and hemogram parameters between both groups.

	Sarcoidosis group N: 716	ILD group N: 323	
age	49±14	60±17	<0.001
gender (% female)	67	57	<0.001
WBC	7567±2853	11458±10678	0.001
Neutrophyl	4910± 2530	9690±12520	0.001
Monocyte	530±280	970±1160	0.001
Lymphocyte	1890±770	3030±2720	0.001
Hb(gr/dl)	13.1±1.56	12.9±1.7	0.29
Hct	39.4±4.4	39.0±4.9	0.52
MCV	84.7±6.6	85.8±7.6	0.12
Plt	260.5±80.5	268.0±79.4	0.38
MPV	8.61±0.94	8.53±1.0	0.47

WBC: white blood cell, Hb:hemoglobin, HCT:hemotocyrte, MCV: mean corpuscular volume, PLT: Platelet, MPV: Mean platelet volume

Table 2. The comparison of ACE, C-reactive protein, sedimentation, NLR ve platelet/Mean Platelet Volume(MPV) values in both groups

	Sarcoidosis group N: 716	Interstitial lung disease group N:323	P value
CRP(IQR)	9.0 (3.3-16.6)	5.1 (3.3-17.4)	>0.005
Sedimantation	25(15-46)	30(15-65)	>0.005
ACE	52(31-75)	49(32-81)	>0.005
Platelet/MPV(IQR)	29.2(23.5-36.0)	31.0(24.1-38.0)	>0.005
NLR(IQR)	2.4(1.7-3.4)	2.5(1.7-4.4)	>0.005

Values median, IQR (interquartilerange) CRP:C-reactive protein, ACE: angiotensinconvertingenyzme, NLR:neutrophiletolymphocyte, MPV: mean platelet volume

The CRP, sedimentation, ACE values were similar in both groups (Table 2).

DISCUSSION

NLR has become popular as a new inflammatory marker. In our study we investigated the status of NLR in sarcoidosis and interstitial lung diseases on the first admission and we identified that the white cell count, neutrophil and lymphocyte count were significantly higher in the interstitial lung disease group than in the sarcoidosis group. On the other hand, the NLR value calculated for the sarcoidosis group was lower than the interstitial group and was not statistically significant.

Age

It has been reported that Sarcoidosis often manifests in young adults and it peaks in patients between the ages 20 and 39 (11). In the ATS/ERS/WASOG 1999 Statement on Sarcoidosis it was reported that, the disease showed a predilection under the age of 40, peaking in those aged between 20-29; but in Scandinavian countries and Japan there was a

second peak of incidence in women over the age of 50 (12). InthestudyconductedbyKıter and colleagues the mean age of sarcoidosis patients was reported as 43 (13). In the ACCESS study, the peak age group was reported as 35-45 age (14). In the study conducted by Gribbin and colleagues, it was reported that most of the patients were between the ages 33 and 55 (15). The mean age of the patients included in our study is consistent with literature.

In patients with interstitial lung disease the mean age is generally reported as 50 years and older (16,17). In Hyldgaard's study conducted in Denmark they reported that the mean age of patients diagnosed with interstitial lung disease was 61±14 (16). In the multicentric study conducted by Müsellim and colleagues that included over 2000 patients newly diagnosed with interstitial lung diseases the mean age was reported as 52±16 (17). The mean age of interstitial lung disease patients in our study is similar to literature and was much higher than the mean age of sarcoidosis patients in consistence with literature.

Gender

The rate of female sarcoidosis patients has been reported higher than male patients. While the rate of female patients in the ACCESS study was reported as 63.6% (14), in the study of Müsellim and colleagues the female – male ratio was reported as 67.6% (18). In lung diseases the female male ratio is similar or in favor of male patients? Szafranski and colleagues have reported the male female ratio as 4.7:1 in their study on interstitial lung diseases (19). In the study conducted by Müsellim and colleagues that investigated the epidemiology and distribution of interstitial lung diseases in Turkey, it was reported that the portion of male patients diagnosed with interstitial lung disease was much larger in the patient group over 50 than the patient group under 50 (17). In our study the ratio of female patients was identified higher similar to literature. In the interstitial patient group, the female - male ratio was similar. The ratio of female patients was higher in the sarcoidosis group than the interstitial group and this difference was statistically significant.

ACE levels

ACE is used as a diagnostic and prognostic marker in sarcoidosis patients. However, it is not specific to sarcoidosis. Depending on the extent and activity of the disease it increases in some of the patients (20,21). In our study, the ACE levels we identified were mildly elevated and no significant difference was observed between the groups. Because we were unable to confirm the stages of sarcoidosis the correlation between ACE levels and the disease stage was not evaluated.

NLR

NLR is a new inflammation marker. There are studies that point to a relationship between prognosis and cardiovascular diseases and malignities (22,23,24,25,26). Studies conducted on chest diseases show that NLR is associated with poor prognosis for lung cancers and mesotheliomas (22,23,27). İliaz and colleagues from our country investigated the value of NLR in the differential diagnosis of tuberculosis from sarcoidosis and identified the NLR value as 2.48 ± 1.1 for sarcoidosis patients. On the other hand, the NLR value of tuberculosis patients was statistically significantly higher than the NLR value of sarcoidosis patients. The NLR values were higher than the control group in both the tuberculosis and sarcoidosis patients. They defined a NLR cut-off value for the differentiation of tuberculosis and sarcoidosis. They reported that NLR values of 2.55 and higher could differentiate tuberculosis from sarcoidosis with an accuracy rate of 76% (6). In the study conducted by Dirican and colleagues the NLR values of sarcoidosis patients was higher than the control group and it was identified that high NLR values were

more common in sarcoidosis patients with extrapulmonary involvement (9). The NLR values identified in our study were similar to the values of İliaz and Dirican's studies. However, we did not identify any meaningful differences between the NLR values of interstitial lung disease patients and sarcoidosis patients. In our study the white cell count, the neutrophil and lymphocyte count was higher in the interstitial patient group than the sarcoidosis group. The other parameters evaluated, hemoglobin, hematocrit, thrombocyte, MCV, CRP and sedimentation values in both groups were similar.

Limitations

Our present study has certain limitations. Firstly, it is a single center study with a retrospective nature. However, our large sample size does provide valuable information. Secondly, our database was created with information obtained from the hospital's automation system and we were unable to perform detailed clinical and radiological evaluations to identify the disease activity. On the other hand, study data comparing NLR values in sarcoidosis and interstitial lung disease patients are limited in literature. We believe the results we obtained from the database of our hospital that is one of the top reference centers in chest diseases in our country will provide insight for future studies.

As a result, it is difficult to say that the NLR values of patients at hospital admittance benefit the doctor in differentiating sarcoidosis and interstitial lung diseases depending on our study results. The NLR values may be similar because both diseases are of noninfectious origin. We recommend planning future studies to investigate the value of NLR in patient monitoring, not differential diagnosis.

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