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Evaluation of frailty and neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios relationship in elderly people

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ABSTRACT

It was aimed to evaluate the relationship between frailty and inflammation in people receiving home health care. It was a cross-sectional study. Edmonton Frail Scale was used to determine the level of frailty and, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were used to determine inflammation. Of 332 people included in the study, 54.82% were females and 45.18% were males. Participants' ages were between 65 and 106. When we examined the frailty of the participants according to the Edmonton Frail Scale, the mean score was 9.403 ± 2.032. The mean neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio of the participants were 4,397±5,038 and 169,363±101,461 respectively. Accordingly, neutrophil-to-lymphocyte ratio was high in men, frail elderly, 75–84 age range, hypertension patients, malnutrition patients; and neutrophil-to-lymphocyte ratio was low in diabetes mellitus, dementia, cerebrovascular accident and hemiplegia. Platelet-to-lymphocyte ratio, another inflammatory marker, was high in men, non-frail elderly, 75–84 age range, hypertension patients and cerebrovascular accident patients; it was low in hemiplegia, malnutrition, dementia, diabetes mellitus. In the study, no statistically significant difference was found between Edmonton Frail Scale and inflammatory markers. More studies are needed on this subject. In addition, we think that examining NLR and PLR values will be useful for monitoring inflammation in frail elderly.

Keywords: frailty, frail elderly, inflammation, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

Abbreviations:
CRP: c-reactive protein
CVA: cerebrovascular accident
DM: diabetes mellitus
HT: hypertension
NLR: neutrophil-to-lymphocyte ratio
PLR: platelet-to-lymphocyte ratio
SD: standard deviation
WBC: white blood cell

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INTRODUCTION

Inflammation, which is the series of reactions of living tissues against cell damage, can be classified into two groups as acute and chronic inflammation. Chronic inflammation, which is thought to develop due to reasons such as inappropriate foods, environmental toxins, obesity, emotional stress, and age, becomes ground for the development of many diseases. Diabetes mellitus (DM), rheumatic diseases, inflammatory bowel diseases, coronary artery diseases, allergies, multiple sclerosis, Parkinson's, and frailty are associated with chronic inflammation.[1,2]

Tissue destruction is often seen in chronic inflammation results in angiogenesis and fibrosis.[1,2] Fibrosis in particular is thought to be one of the causes of frailty in elderly people. Frailty may cause an increase in geriatric syndrome findings such as falls, immobilization, chronic pain, and depression in the elderly. Frailty in old age is an important cause of mortality and morbidity.[3,4]

While acute inflammation is replaced by chronic inflammation, the neutrophil count decreases; the number of macrophages, lymphocytes and plasma cells increases. Therefore, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which are new markers of inflammation, are expected to increase in acute inflammation and decrease in chronic inflammation. There are studies that examining the relationship between NLR and PLR with some diseases.[5,6] Some of these studies found a positive correlation between the disease and NLR-PLR, while others found a negative correlation.[7] However, NLR-PLR levels in the frail elderly have not been compared with those in the non-frail. If chronic inflammation is the primary cause of frailty in the elderly, a decrease in NLR and PLR is expected. On the other hand, if chronic inflammation is not the primary cause of frailty, the NLR and PLR levels of the frail elderly may be higher, lower, or the same as the non-frail elderly.

Studies have reported that interleukin-6, C-reactive protein (CRP), fibrinogen, factor 8, which are inflammatory markers, have increased in frail elderly patients.[8] Nowadays, NLR and PLR which are increasingly used as inflammatory markers, are easy to access and apply, inexpensive, and common examinations.

It was aimed to evaluate the relationship between frailty and inflammation in people receiving home health care. For this reason, the Edmonton Frail Scale was used to determine the level of frailty and, NLR and PLR were used to determine inflammation. The research hypotheses are as follows:

H_0: There is no relationship between inflammation and frailty.

H_1: There is a relationship between inflammation and frailty.

METHODS

The article is cross-sectional research. The health records of people who received home health care services from Antalya Training and Research Hospital between 01 Nov 2017 and 30 Apr 2020 were retrospectively reviewed. The examined laboratory markers of the participants who met the inclusion criteria, were obtained from the health records. Then, between 05 Jan 2020-06 March 2020, the Edmonton frail scale was applied to the participants and/or their caregivers by authors. Written permission was obtained from the participants or their caregivers.

Edmonton Frail Scale used in the study was developed by Rolfson et al, and it includes 11 questions and investigates the frailty of the elderly.[9] NLR and PLR, which are used as inflammation markers in the research, are markers that can be easily calculated with the help of a hemogram, result in a short time, and their use is increasingly common.

This study was approved by the Ethics Review Committee of our center (2019-12/30). The

study was conducted in accordance with the Helsinki Declaration.

Inclusion criteria in the study were having received home health care between 01 Nov 2017 and 30 Apr 2020, being 65 years of age and over, having had a hemogram test within the scope of home health care service within the specified date range, being agreed of the patient himself and/or his caregiver to answer the Edmonton frail scale questions. Exclusion criteria were not having received home health care between 01 Nov 2017 and 30 Apr 2020, being under 65 years of age, not having a hemogram test within the specified date range, and refusing the patient and/or caregiver to answer Edmonton Frail Scale questions.

The sample size was not determined in the study, and all participants who met the inclusion criteria were included in the study. There were 332 participants in total. In the statistical analysis, the IBM SPSS 22.0 version was used and p values less than 0.05 were considered statistically significant.

Number and percentage were used in defining categorical data, mean, standard deviation, median, variance, minimum, and maximum were used in defining numerical data. Pearson correlation coefficient was calculated to investigate the correlation between continuous data. The compliance of the data to normal distribution was evaluated using the Shapiro-Wilk test. Kruskal-Wallis Test or Mann Whitney U test was used for the evaluation of numerical data, and chi-square and Fisher tests were used for the evaluation of categorical data.

RESULTS

Of 332 people included in the study, 182 were females (54.82%) and 150 (45.18%) were males. Participants' ages were between 65 and 106 and the mean age was 81.162 ± 8.483. Of the participants 324 (97.6%) had at least one chronic disease. The most common chronic diseases were hypertension (n=153, 46.1%), dementia (n=93, 28.0%), DM (n=92, 27.7%), malnutrition (n=75, 22.6%), cerebrovascular accident (CVA) (n=62, 18.7%), hemiplegia (n=50, 15.1%).

Of the participants 3 (0.9%) were employed, 31 (9.3%) were unemployed and had no income, 298 (89.8%) were retirees.

When we examined the frailty of the participants according to the Edmonton Frail Scale, the mean score was 9.403±2.032. According to the Edmonton Frail Scale, 0–5 points were considered not frail, 6–7 apparently vulnerable, 8–9 mildly frail, 10–11 moderately frail, 12 and above severely frail (6). According to this, 8 people (2.4%) were not frail, 27 people (8.1%) were apparently vulnerable, 60 people (18.1%) were mildly frail, 135 people (40.7%) were moderately frail, 102 people (30.7%) were severely frail. In other words, 35 (10.54%) people were not frail, while 297 (89.46%) people were frail.

When examining the NLR-PLR distributions according to the gender of the participants, the mean NLR and PLR of females were 4.139±5.143 and 158.301±90.378, respectively, while the mean NLR and PLR of males were 4.71±4.908 and 182.784±112.319, respectively (p=0.076 and p=0.117).

When the correlation between Edmonton score and NLR, PLR, WBC was examined, the results were statistically insignificant. The r and p values are respectively: (r=0.085 and p=0.122), (r=–0.04 and p=0.465), (r=0.097 and p=0.079).

The distribution of the laboratory parameters of the participants we investigated was as in Table 1.

The relationships between frailty and NLR, PLR, WBC were examined. The distribution was as in Table 2.

Table 1 The descriptive statistics of laboratory parameters

	Mean	Median	SD	Variance	Minimum	Maximum
Hemoglobin	11.558	11.5	1.851	3.43	5.7	17.4
Hematocrit	35.437	35.5	5.586	31.205	18.5	53.5
Neutrophil	6.265	5.15	3.961	15.697	0.9	28.2
Platelet	269.518	247.5	109.738	12042.57	12	643
Lymphocyte	1.928	1.7	1.288	1.66	0.4	19.6
MCV	86.03	86.3	8.455	71.502	57.5	108.9
WBC	9.047	8.1	4.138	17.128	2.3	34.1
RBC	4.196	4.1	1.004	1.009	1.8	14.7
NLR	4.397	3	5.038	25.391	0.2	42.4
PLR	169.363	147.513	101.461	10294.53	7.69	712

SD: standard deviation
MCV: mean corpuscular volume
WBC: white blood cell
RBC: red blood cell
NLR: neutrophil-to-lymphocyte ratio
PLR: platelet-to-lymphocyte ratio

Table 2 The relationships between frailty and inflammatory markers

	NLR		PLR		WBC	
	Mean± SD	p	Mean± SD	p	Mean± SD	p
Frail* (n=297)	4.454±5.229	0.846**	167.046±101.216	0.128**	9.084±4.211	0.663**
Not frail* (n=95)	3.908±2.965		189.021±102.882		8.737±3.498	

*Scoring for Edmonton Frail Scale: Not Frail:0–5. Apparently Vulnerable:6–7. Mildly Frail: 8–9. Moderate Frailty:10–11. Severe Frailty: 12–18. (So, Not Frail:0–7 and Frail:8–18)
**Mann Whitney U Test
NLR: neutrophil-to-lymphocyte ratio
PLR: platelet-to-lymphocyte ratio
WBC: white blood cell
SD: standard deviation

When the age groups and NLR-PLR relationships of the participants were examined, it was found that both mean values of NLR and PLR increased in the middle-old age at 75–84 age range (Table 3).

Table 3 The relationships between age and NLR-PLR relationships

Age groups		NLR		PLR	
		Statistic	p	Statistic	p
Youngest-old, 65 to 74 (n=84)	Mean	4.0974	0.016*	178.0907	0.147*
	SD	3.56591		91.78405	
Middle-old, 75 to 84 (n=125)	Mean	4.9751		179.0354	
	SD	6.8237		121.84537	
Oldest-old, ≥85 (n=123)	Mean	4.0147		153.5731	
	SD	3.5157		81.91216	

* Kruskal-Wallis Test
NLR: neutrophil-to-lymphocyte ratio
PLR: platelet-to-lymphocyte ratio
SD: standard deviation

The comparison of NLR-PLR relationships with the most common chronic diseases of the participants was shown in Table 4.

Table 4 The comparison of NLR-PLR relationships with the most common chronic diseases

Chronic Disease		NLR		PLR	
		Mean± SD	p	Mean± SD	p
Arterial Hypertension	No (n=179)	4.0952±4.59619	0.056*	162.4326±107.16235	0.015*
	Yes (n=153)	4.7505±5.50652		177.4712±94.05773	
Diabetes Mellitus	No (n=240)	4.7591±5.73058	0.598*	177.9698±111.06560	0.083*
	Yes (n=92)	3.4532±2.2051		146.9107±65.89468	
Dementia	No (n=239)	4.5572±5.5903	0.590*	175.7967±109.08514	0.139*
	Yes (n=93)	3.9860±3.2049		152.8292±76.61847	
Malnutrition	No (n=257)	4.3090±5.1921	0.358*	170.0474±99.18753	0.443*
	Yes (n=75)	4.6994±4.4939		167.0179±109.5683	
Cerebrovascular Accident	No (n=270)	4.4275±5.3057	0.224*	168.6264±101.0994	0.212*
	Yes (n=62)	4.2654±3.6904		172.5710±103.7993	
Hemiplegia	No (n=282)	4.5879±5.3464	0.074	171.2042±101.7980	0.212*
	Yes (n=50)	3.3217±2.4927		158.9787±99.9165	

*Mann Whitney U Test
NLR: neutrophil-to-lymphocyte ratio
PLR: platelet-to-lymphocyte ratio
SD: standard deviation

When the frailty by gender was evaluated, the mean Edmonton score of males was 9.186±2.115 and the Edmonton score of females was 9.582±1.950 (p=0.058).

The comparison of the employing status of the participants by the frailty groups was given in Table 5.

Table 5 The comparison of the employing status of the participants by the frailty groups

		Employing Status			Total	p
		Employed (n)	Unemployed (n)	Retired (n)		
Edmonton Groups (Edmonton Frail Score)	Not Frail (0–5)	2	0	6	8	0.000*
	Apparently Vulnerable (6–7)	0	6	21	27	
	Mildly Frail (8–9)	1	3	56	60	
	Moderate Frailty (10–11)	0	17	118	135	
	Severe Frailty (12–18)	0	5	97	102	
Total		3	31	298	332	

* Chi-Square Tests

There was a positive correlation between the Edmonton scores and ages of the participants (r=0.115 and p=0.036). The Edmonton score was distributed as a mean value of 9.119±2.044 in the young elderlies between the ages of 65–74, as a mean value of 9.352±2.083 in the middle-aged elderlies, and as a mean value of 9.650±1.958 in the advanced-aged elderlies.

We compared the participants' common chronic diseases with their Edmonton scores. The mean Edmonton score of participants with hypertension (HT) was 9.692±1.857 and without hypertension was 9.156±2.145 (p=0.07).

The mean Edmonton score of participants with diabetes was 9.739±2.08, and without diabetes was 9.275±2.2 (p=0.115).

Participants with dementia had a mean Edmonton score of 10.44±1.528 and participants without dementia had a mean Edmonton score of 9.000±2.064 (p=0.000).

Participants with malnutrition had a mean Edmonton score of 10.76±1.54 and participants without malnutrition had a mean Edmonton score of 9.007±1.99 (p=0.000).

Participants with CVA had a mean Edmonton score of 10.338±1.366 and participants without CVA had a mean Edmonton score of 9.188±2.1 (p=0.000).

Participants with hemiplegia had a mean Edmonton score of 10.1±1.515, and participants without hemiplegia had a mean Edmonton score of 9.280±2.089 (p=0.015).

DISCUSSION

Of the elderly in our study, 89.5% were frail and a large part of the frail elderly was in the moderately frail group, only 10.5% of our participants were in the non-frail group. In a comprehensive study investigating the prevalence of frailty in Turkey, it has been stated that the frailty rate was 44.5% for females over 65 years of age and 29.0% for males.[10] The higher rates of frailty in our study may be a result of the selection of the participants among those

receiving home health care services.

In our study, the mean NLR and PLR of the participants were quite high, the mean NLR was 4,397±3,000 and the mean PLR was 169,363±147,513. In a study investigating the NLR and PLR values of participants over the age of 70, the mean NLR of the participants was 2.734.[11] In a study investigating the inflammatory markers of patients with ankylosing spondylitis, the mean NLR was 1.30±0.16 and the mean PLR was 94.98±17.96 in the control group consisting of healthy volunteers.[12] This situation may be related to the age, gender distribution and chronic diseases of the patients included in the study. Therefore, it is important to determine the cut-off values for each variable of NLR and PLR, which may vary in relation to many parameters.

In this study, females had lower NLR and PLR mean values than males. In a study conducted in China, while the mean NLR of females between the ages of 30–49 was higher than that of males, similar to the results of our study, the mean NLR of females between the ages of 60–69 was lower than that of males. However, PLR was higher in females than males in all age groups.[13] In a study investigating the NLR values in different age groups, it has been concluded that the NLR can vary by age group and gender. According to the results, while the mean NLR of females aged 30–59 was higher than males, in people aged 60 and over, the mean NLR of females was lower than that of males.[11] When evaluating the results of inflammatory markers, age and gender-related change should be considered, especially in elderly patients.

In our study, the changes of inflammatory markers according to frailty were examined. Accordingly, as the frailty of the participants increases, the NLR and WBC means increase; PLR mean was decreasing. However, the results were not statistically significant. Similar to our study, in another study examining the relationship between inflammation and frailty, the mean NLR in the frail elderly has been found to be higher than in the non-frail elderly. The mean values were 2.41 and 2.17.[3] In another study that performed geriatric evaluation in elderly patients with cancer, a positive correlation has been found between frailty and NLR.[14]

In our study, some chronic diseases and NLR and PLR levels were examined. Accordingly, NLR increased in HT and malnutrition, but NLR decreased in DM, dementia, CVA and hemiplegia. Besides this, PLR increased in HT and CVA, but PLR decreased in DM, dementia, malnutrition and hemiplegia. The etiology of all the diseases we examined in our study is multifactorial. If there was only chronic inflammation in the etiology, we would expect NLR and PLR to decrease in all diseases.

NLR and PLR were increased in patients with HT. In studies evaluating the relationship between HT and NLR and/or PLR, the results were similar to our study. In a study that evaluated individuals with HT and developed end-organ failure and two groups with HT but not developed end-organ failure in terms of NLR; the mean NLR in individuals with end-organ failure has been found to be 4.12±4.76 and the mean NLR in people without end-organ failure has been found to be 2.23±1.54.[15] In a study comparing newly diagnosed HT patients and healthy volunteers, the mean NLR in newly diagnosed HT patients was 3.14±2.16, while the mean NLR in healthy volunteers was 1.89±0.90 ($p<0.001$). The mean age of the participants was 44.[16] In another study, the NLR and PLR have been found to be higher in frail patients with coronary artery disease compared to those who were not.[17]

In our study, NLR and PLR were decreased in people with DM. In a study investigating the relationship between DM and NLR, while the NLR was 2.18±0.61 in newly diagnosed type 2 diabetes mellitus (T2DM), without complications, the mean NLR was statistically significantly increased in DM 2 patients with peripheral neuropathy, the mean NLR was 2.58±0.5. In this study, the mean age of both groups was 62.351.[18] In another study evaluating the relationship between DM and NLR, it has been found that the mean NLR increased in DM 2 individuals. The mean age of the DM group in this study was 58.6±10.9, while the mean age of the healthy

control group was 39.2±12.4 years.[19] In the same study, the mean NLR in the DM group has been found to be 2.44 and 1.5 in the control group.[19] The mean NLR in gestational DM was 3.00±0.83 and the mean NLR in females without it was 2.26±0.43, and $p<0.001$.[20]

NLR and PLR were decreased in our participants with dementia compared to participants without dementia. In a study conducted with the elderly with Alzheimer's or major depression or Parkinson's disease, the NLR level has been found to be significantly higher in patients with Alzheimer's dementia compared to other groups.[21] We think that the incompatibility of research results may be caused by other diseases of the people included in the study. In order to make a decision about this issue, it is necessary to conduct comprehensive research with groups close to each other in terms of sociodemographic and chronic diseases.

In our study, NLR increased and PLR decreased in malnutrition. Similar to our study, in a study conducted with 95 elderly people, the mean NLR was 2.4±0.9 in the elderly with malnutrition, while the mean NLR in the elderly without malnutrition has been found to be 1.8±0.7 ($p=0.004$).[22]

In our study, the mean NLR in patients with CVA and hemiplegia was decreased compared to those who did not have a disease. PLR increased in CVA patients but decreased in hemiplegia patients. Similar to our study, according to a study examining the status of inflammatory markers in patients with acute pulmonary embolism, as the severity of the disease has increased in patients with acute pulmonary embolism, the mean NLR and PLR have decreased.[23] This situation shows the clinical importance of its decrease as well as the increase in inflammatory markers NLR and PLR.

In our research, females were frailer than males. Similar to our study, Fried et al in their study, Nakano et al in their study, and Pegorari et al in their study have found higher frailty in females than males. The reasons for this may include the fact that females have more chronic diseases and their burden of providing care, as well as the longer life expectancy of females.[24-26]

Chronic inflammation and fibrosis that increase with age are among the important causes of frailty. Therefore, a positive correlation is expected between frailty and age. Similar to our study, in the study of Doğrul et al, and Nakano et al, a positive correlation was found between frailty and age.[3,26]

We compared the most common chronic diseases in the participants and the frailty of the participants one by one. Accordingly, those with HT were frailer than those without HT. But the result was statistically insignificant. Similar to our study, in the study of Fried et al, among the elderly aged 65–101 years, those with HT have been found to be frailer than the others.[24] Again, according to the results of Nakano et al's study, the frailty of the elderly with HT was higher.[26]

Those with DM were more frail than our participants without DM. But the result was statistically insignificant. Similar to our study, in the cohort study of Pahwa et al, elderly patients with DM were more vulnerable than those without DM.[1] There are different studies in the literature that showed a relationship between DM and frailty.[18]

Our participants with dementia were more frail than those without dementia and the result was statistically significant. Similarly, a statistically significant relationship has been found between dementia and frailty in the study of Doğrul et al.[3]

Of the chronic diseases we investigated, those with malnutrition were frailer than those without and the result was statistically significant. In a study with 206 participants, which investigated the relationship between nutrition and frailty in the elderly, a strong relationship has been found between frailty and malnutrition.[27]

In our study, those with CVA were frailer than those without and the result was statistically significant. Similar to our study, frailty was found to be higher in patients with CVA in studies on frailty.[3,26]

Again, according to our results, patients with hemiplegia were frailer than those without hemiplegia and the result was statistically significant. In the study of Looman et al, parallel to our study, there has been a relationship between hemiplegia and frailty. Namely, 24.1% of 1516 multi-frail elderly people included in the study had a stroke, brain hemorrhage, cerebral infarction, or transient ischemic attack.[28] According to another study, there was a two-way relationship between frailty and stroke in the elderly. In other words, while age, comorbidity, and frailty increase the risk of stroke, the frailty of the elderly who had a stroke was also increasing.[29]

In all chronic diseases, we examined one by one, the elderly with the disease were frailer than those who did not have a disease. Because, whether it has an effect on morbidity, chronic diseases negatively affect the quality of life of people, thus causing an increase in frailty in the elderly.

In our study, the laboratory results of the patients were reached by reviewing the health records between 11 Jan 2017 and 30 Apr 2020. However, the Edmonton Frail Scale was applied between 05 Jan 2020-30 March 2020 after these recordings were taken. The fact that both evaluations cannot be made at the same time is the limitation of the study.

There are many studies showing a relationship between frailty and inflammation in the elderly.[3,8,14] As also a result of our research, a positive correlation was found between NLR and frailty, and a negative correlation between PLR and frailty. However, our results were not statistically significant. More studies are needed on this subject. In addition, we think that examining NLR and PLR values will be useful for monitoring inflammation in frail elderly.

CONFLICTS OF INTEREST STATEMENT

The authors declare that they have no commercial interests.

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