Original Paper

The Role of Neutrophil to Lymphocyte Ratio in the Assessment and Rehabilitation of Knee Osteoarthritis Patients

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ABSTRACT: Osteoarthritis (OA) is considered to be a real problem for many people. The last decade is characterized through an increased interest in using a non-specific, simply and readily available marker of inflammation-neutrophil to lymphocyte ratio (NLR)-to predict various chronic diseases (gastrointestinal and colorectal cancers, lung cancer, cardiovascular events, sarcoidosis, arthritis). The aim of our study is to establish the correlation between NLR and other parameters of clinical and functional status in KOA patients and to compare the NLR values before and after rehabilitation program. 90 patients, aged 40 to 82 years, diagnosed with mild (8 patients), moderate (70 patients) and severe (12 patients) KOA, in accordance with Kellgren and Lawrence score. Statistical assessment showed different values for the erythrocyte sedimentation (ESR) rate at 1-hour, Visual Analogue Scale (VAS), and Lequesne index in the studied group. NLR regression was significant for ESR at 1 and 2 hours. As an independent diagnostic marker, NLR has limited value, however it can be considered an inexpensive additional biomarker for the diagnosis of KOA and for monitoring the rehabilitation program.

KEYWORDS: *NLR, osteoarthritis, knee.*

Introduction

Osteoarthritis (OA) is considered now almost unanimously to be a real problem for many people. The definition used for OA is complex and tries to include heterogeneity of this disease from epidemiological, etiology, pathogenic, clinical and functional points of view:

- OA is one of the most prevalent and debilitating chronic diseases worldwide, affecting predominantly older adults [1];
- OA is a highly prevalent rheumatic musculoskeletal disorder; the most commonly affected appendicular joints are the knee, hip and hand [2]. This serious disease, which affected 303 million people globally in 2017, has a considerable impact on the individual patient, resulting in pain and disability [3];
- if four decades ago, OA was considered a ‘‘wear and tear’’ disease or degenerative joint disease, at present OA involves metabolic and inflammatory components, depending on the cause of osteoarthritis initiation [4,5], and oxidative damage with overproduction of reactive oxygen species (ROS) [6];
- OA is a multifactorial disease involving all structures of the joint, including cartilage (progressive cartilage matrix degradation), bone (subchondral bone sclerosis and osteophyte formation), ligaments, muscles, tendons, menisci, synovium (synovial inflammation), and the synovial fluid [4,7].

All these joint structure changes lead to pain, stiffness, swelling, and loss of normal joint function [2].

Similar to the variety of definitions of this condition (OA) is the diversity of pathogenic theories, formulated especially in recent years.

OA is characterized by a pathology involving the whole joint; the variety of potential molecular and cellular changes is involved in the joint destruction process [8].

Pathogenic pathways include aging, genetic predisposition [7], mechanical loading conditions, metabolic (obesity) and inflammatory components, in close correlation with the loading environment, and the lifestyle of patient [4].

It is increasingly recognised that knee osteoarthritis (KOA) is of the most common and severe forms of osteoarthritis, followed by the hand and hip.

Described as a complex multifactorial and polygenetic disease involving structural and functional alterations of the entire joint [9] and one of the leading contributors to global chronic disability, KOA is characterized by joint pain and stiffness leading to functional limitations and loss in participation and quality of life [10].

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The prevalence of KOA is increasing worldwide, has enormous health-care impact and entail a high cost to society.

Although it is most prevalent in the elderly population (affecting approximately 33% of the people aged 60 to 70, and about 44% above the age of 80 years) [4] and in persons with traumatic joint injuries [11] there is an increasing trend of young adults (under 55 years old) being diagnosed with KOA, estimated to affect one in eight adults.

KOA represents now one of the major causes of disability worldwide, with reduced mobility of the entire population, women being twice as affected compared with men [12].

The knee is a complex joint, with mechanical and biological functionalities that can be difficult to separate.

Even though a number of risk factors for KOA are well known (age, female sex, obesity, injury, muscle weakness and malalignment) [5,13] the pathogenesis of this entity is unclear.

The cellular and molecular events from chondrocytes [14], abnormal synovial changes, morphological and biochemical disruptions of subchondral bone [13] of which lead to KOA signs and symptoms (knee pain and stiffness, tenderness, and swelling, disability and gait disturbing, impairing quality of life) [7] are neither well understood nor easily measurable.

Latest data mentioned that inflammation has an important role in KOA pathogenesis.

It is considered that the release of pro-inflammatory mediators (cytokines, adipokines, and growth factors) determines the inflammatory responses in joint tissues, with the loss of normal structure and function [15].

The use of biomarkers for OA and other nonspecific marker of inflammation can determine early disease, and identify the progression grade, with a real benefit for rehabilitation program.

Recent studies reported a change in numbers of lymphocytes, neutrophils, monocytes, and platelets are significantly altered during inflammation [16].

The last decade is characterized through an increased interest in using a nonspecific, simply and readily available marker of inflammation-neutrophil to lymphocyte ratio (NLR)-to predict various chronic diseases (gastrointestinal and colorectal cancers, lung cancer, cardiovascular events, sarcoidosis, arthritis) [17,18,19].

The neutrophil/lymphocyte ratio (NLR) is calculated by dividing the absolute neutrophil count by the lymphocyte count obtained from a complete peripheral blood count.

Furthermore, the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) can reflect the balance of the immune response, and were reported to be independent and inexpensive predictors of many inflammatory and immune diseases the diagnostic value of the NLR and PLR in KOA.

It is considered that a blood NLR ≥2.1 had 50% sensitivity and 77% specificity for predicting severe knee OA [20].

More recently, it has been proposed as an independent factor to predict hip and knee radiographic severity, as well as modulate the postoperative period after arthroplasty [21].

However, none of these studies examined the association between NLR and functional status in patients with primary KOA and if the rehabilitation program influences the NLR value.

So, the aim of our study is both to establish the correlation between NLR and other parameters of clinical and functional status in KOA patients and to compare the NLR values before and after rehabilitation program.

We respected the actual international management recommendations for KOA [22].

Material and Methods

The approval from Craiova University of Medicine and Pharmaceutical Ethics Committee was obtained (no. 138/07.12.2020) according to the recommendations contained in the Declaration of Helsinki on Biomedical Research Involving Human Subjects as revised in 2013.

All subject's participant in our study signed an informed consent.

Between 2022 and 2023, a cohort encompassing 90 individuals, all of whom had undergone clinical diagnosis for KOA, was established within the Rehabilitation Department of the "Filantropia" Hospital in Craiova.

We took into consideration the following eligible criteria for our patients:

- aged more than 40 years;
- no knee injuries in the last 6 months;
- no major disturbances of the knee's frontal plane alignment;
- diagnosed with unilateral or bilateral KOA according to the criteria of clinical and radiographic findings by the American College of Rheumatology (ACR) [2];
- without surgical treatment for KOA;
- patients with other co-morbidities, but well controlled, like: arterial hypertension, dysplipemia and mellitus diabetes type II; a

history of a symptomatic or complicated upper gastro-intestinal ulcer;

- no medication like steroids, immunosuppressive or psychotropics drugs;
- able to independently ambulate without any walking aids in the community;
- compliance with physical exercise during the healthcare program.

We excluded people with any history of acute or chronic infections, autoimmune or hematologic diseases, other neuromuscular disorders of the lower limbs, visual deficits or uncontrolled cardiopulmonary disease that may interfere with balance and walking.

We performed etiopathogenic, clinical, lab screening and functional evaluation (lab-screening, x-raying).

After etiopathogenic and clinical assessment, we conducted a laboratory and radiological examination of the knee.

Patients assessment was performed on two levels-first (T1) and after another 4 weeks (T2) in the outpatient environment-during which the in-hospital rehabilitation program was carried out.

The studied parameters were:

- Body Mass Index (BMI)-was calculated as the ratio of body weight (kg)/height (m2);
- erythrocyte sedimentation rate in 1 hour (ESR1);
- erythrocyte sedimentation rate in 2 hours (ESR2);
- C-Reactive Protein (CRP) and fibrinogen;
- NLR=neutrophil-to-lymphocyte ratio (NLR);
- Visual Analogue Scale (VAS);
- Lequesne index;
- WOMAC scale.

Blood specimens for laboratory analyses were carefully obtained from all patients' antecubital vein after overnight fasting and under all aseptic precautions.

The blood routine tests were performed by two automatic blood analyzers (MINDRAY BC-6800 for blood test, ARCHITECT C4000 for biochemical analysis, SYSMEX CS-25001 for fibrinogen).

Standard reference values were used for the interpretation of all parameters (neutrophils 2.0-8.0×10^3/μL, lymphocytes 1.8-4.5×10^3/μL, platelets 150-450×10^3/μL, and monocytes 0.00-1.00×10^3/μL; CRP 0-0.5 mg/dL, fibronogen 170-420mg/dl and ESR 4-9mm/h).

The neutrophil/lymphocyte ratio (NLR) is calculated by dividing the absolute neutrophil count by the lymphocyte count obtained from a complete peripheral blood count.

The Kellgren and Lawrence Radiographic KOA (KL) scoring is often measured in grades 0 to 4 based on spatial narrowing and structural bone modifications.

The KL grading was interpreted by a physician based on recent weight-bearing, anterior-posterior X-rays of the tibiofemoral joint for both knees without knowledge of the clinical conditions.

In order to assess the functional parameters, we used the Visual Analogue Scale (VAS) where 0 means the patient has no pain and 10 represents maximal pain.

Values from 0 to 10 are directly proportional to the pain intensity and individual acceptability.

Lequesne Functional Index and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were used for determining the effect the disease has in performing daily living activities.

WOMAC contains 24 specific questions divided into three domains: pain, stiffness, and physical function.

The score of each question ranges from 0 to 4.

The 0 score is equivalent to maximal functional status and high scores 96 indicates a minimum status, with high disruption in day to day tasks [23].

For the Lequesne Index (a 10-item questionnaire) 0 is indicative of less functional impairment or maximum functional status (pain, maximum walking distance, and daily activities) while 24 is the minimum, the worst outcomes.

Lower limb dysfunction is indicated from 0 (none), 4 (mild), 5-7 (moderate), 8-10 (severe), 11-13 (very severe and more than 14 is characteristic for extremely severe limiting and dysfunction [24].

The objectives of rehabilitation program were:

- pain management;
- inflammatory process control;
- correction of the abnormal gait scheme;
- restoration the lower limb functionality;
- preserving and increasing quality of life.

The components of applied rehabilitation program were:

- education and diet recommendation's;
- medication for each co-morbidity and anti-inflammatory drugs;
- physio;
- therapy (electrotherapy-TENS, laser, ultrasound);
- kinetotherapy (daily exercises for motor control and gait).

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Statistic assessment

The data was stored in Excel files (Microsoft, USA).

Descriptive statistics was carried out in Excel, while inferential statistics was carried out in part in Excel, in part in Matlab (MathWorks, USA).

For numerical data, mean±standard deviation (SD) is presented.

Data normality was assessed using the Shapiro-Wilk normality test.

Student's t-test, and One-Way ANOVA were used to assess difference of means between two groups, and more than two groups, respectively.

The Pearson correlation coefficient (r) was uses to assess correlation between numerical data.

The Chi-square test was used to assess correlation on categorical.

A p-value <0.05 was considered statistically significant for all comparisons.

Results

Our study group consisted of 90 patients, aged 40 to 82 (Table 1), diagnosed with mild (8 patients), moderate (70 patients) and severe (12 patients) KOA, in accordance with Kellgren and Lawrence (KL) score.

The sex repartition was 81% females and 19% males, which shows a highly significant difference from the sex repartition in the general population (z score for proportions <0.001).

The urban: rural ratio was 47:43, almost 1, which means there is no influence of the area of residence on the studied condition.

The mean age of the studied group was 66.63 (SD=7.87) years.

Age distribution was almost normal (Anderson-Darling test for normality p=0.521 (W =0,3232) >0.05), but we have to mention that the condition appears after 40 years of age.

Table 1. Demographic data of studied patients.

Biographic data						**Total**
Sex	Female=73 (81%)		Male=17 (19%)			90=100%
Residence	Urban=47 (52%)		Rural=43 (48%)			90=100%
Age	40-49 years	50-59 years	60-69 years	70-79 years	80-89 years	90=100%
	1 (1.11%)	13 (14.44%)	42 (46.66%)	29 (32.22%)	5 (5.55%)	
BMI	Normal	Overweight	Obese I	Obese II	Obese III	90=100%
	0	31 (34.44%)	40 (44.44%)	18 (20%)	1 (1.11%)	
KOA severity	mild		moderate		severe	90=100%
	8 (8.88%)		70 (77.77%)		12 (13.33%)	

Weight distribution was not normal (Anderson-Darling test for normality p=0.0276<0.05), with weights skewed towards higher values, meaning this condition is associated with overweight status.

BMI (body mass index) distribution was not normal (Anderson-Darling test for normality p=0.0389 (W=0.7903) <0.05), with weights skewed towards obesity grade 1 and overweight (Figure 1).

This parameter had a significant correlation with gender, and female patients were characterized by a higher BMI than male.

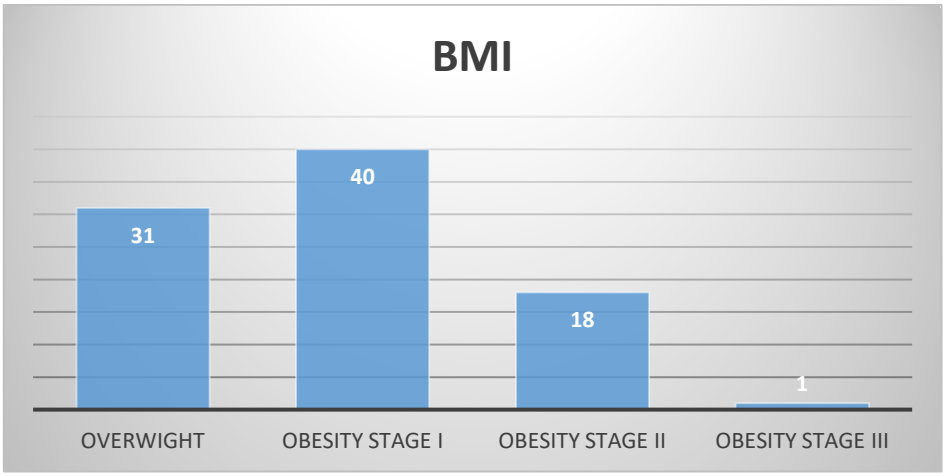

Figure 1. BMI in studied patients.

As comorbidities, we found that there are almost 39% of patients with venous insufficiency, 33% of patients with dyslipidemia and 28% of patients with Diabetes mellitus.

Nearly half (49%) of studied patients had physically demanding job, with the involvement of lower limbs.

Comparing the mean values of the studied parameters (Table 2), for the all patients, we found significant differences only for the values erythrocyte sedimentation rate (ESR1) (p=0.04), VAS (p=0.002) and Lequesne index (p=0.05).

Comparing the values recorded for the mentioned parameters among the two visits (Table 2), in all patients, we obtained a significant difference (p <0.05, test Student) for the same parameters as in the case of establishing correlations (ESR1, p=0.04; VAS, p=0.001 and Lequesne index p=0.04).

Taking into account all parameters for gender (Table 3) and patient's origin (Table 4), we obtained no significant values for correlation (Pearson) or significant differences' (t Student), except for sex BMI, and age and VAS score in T2 for rural / urban patients.

Table 2. The study variables-mean values and SD for all patients.

Parameter	T1 (initial assessment)				T2 (after 4 weeks)			
	Mean	SD	Min	Max	Mean	SD	Min	Max
BMI	32.23	3.43	25.36	41.62				
NLR	2.26	1.72	0.79	9.92	2.03	1.82	0.40	11.19
ESR 1 (mm)	**38.27**$^{*\#}$	22.78	9	85	**28.24** $^{*\#}$	20.03	5	90
ESR 2 (mm)	61.17	29.2	20	120	50.04	29.99	9	130
CRP (mg/dl)	0.53	0.58	0.02	5.3	0.45	0.61	0.06	3.31
Fibrinogen (mg/dl)	343.40	73.30	164	550	329.77	69.61	185	417
VAS	**6.81** $^{*\#}$	0.95	5	9	**5.26**$^{*\#}$	0.82	4	7
Lequesne index	**8.01** $^{*\#}$	2.52	5	14	**7.10**$^{*\#}$	2.07	4.5	12
WOMAC scale	62.13	10.94	42	81	57.74	9.60	45	76

BMI=body mass index, ESR 1=erythrocyte sedimentation rate in 1 hour, ESR 2=erythrocyte sedimentation rate in 2 hours, CRP=C-Reactive Protein, NLR=neutrophil-to-lymphocyte ratio *=Pearson correlation, #=t Student

Table 3. Study variables-mean values and SD / females and male.

Parameter	Female patients				Male patients			
	T1		T2		T1		T2	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	64.29 (SD=7.58) years				67.14 (SD=7.77) years			
BMI	**29.94 (SD=2.86) kg/m2** $^{\#}$				**32.28 (SD=3.43) kg/m2** $^{\#}$			
NLR	3.95	3.72	1.64	0.37	2.31	2.01	1.92	0.72
ESR 1 (mm)	26.20	12.30	22.63	18.52	40.68	23.70	29.47	20.26
ESR 2 (mm)	48.20	18.70	40.62	30.63	63.88	30.54	52.11	29.66
CRP (mg/dl)	0.39	0.34	0.31	0.12	0.53	0.72	0.48	0.66
Fibrinogen (mg/dl)	354.60	53.38	329.35	84.23	346.67	70.72	324.80	72.29
VAS	6.41	1.12	5.20	0.45	6.79	0.93	5.27	0.82
Lequesne index	7.68	2.70	6.6	2.61	8.09	2.48	7.19	2.00
WOMAC scale	59.00	12.42	58.00	12.16	59.95	10.92	57.58	9.30

BMI=body mass index, ESR 1=erythrocyte sedimentation rate in 1 hour, ESR 2=erythrocyte sedimentation rate in 2 hours, CRP=C-Reactive Protein, NLR=neutrophil-to-lymphocyte ratio *= Pearson correlation, #=t Student

Table 4. Study variables-mean values and SD / rural and urban.

Parameter	Rural patients				Urban patients			
	T1		T2		T1		T2	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	**68.44 (SD=6.86) years** $^{\#}$				**64.91 (SD =8.24) years** $^{\#}$			
BMI	31.87 (SD=3.46) kg/m2				31.84 (SD=3.44) kg/m2			
NLR	2.14	2.32	1.89	1.06	2.59	2.12	1.95	1.28
ESR 1 (mm)	33.93	18.07	24.67	20.46	42.06	26.21	31.43	14.30
ESR 2 (mm)	55.15	30.63	43.74	24.57	66.06	70.02	55.68	28.60
CRP (mg/dl)	0.42	0.28	0.31	0.21	0.58	0.88	0.57	0.80
Fibrinogen (mg/dl)	346.77	75.50	324.89	65.97	340.32	71.92	334.03	74.53
VAS	6.91	0.97	**5.60** $^{\#}$	**0.83**	6.55	0.95	**4.94** $^{\#}$	**0.66**
Lequesne index	7.73	2.24	6.56	2.11	8.27	2.41	7.09	2.03
WOMAC scale	60.35	10.95	58.40	10.18	58.04	11.40	57.13	9.13

BMI=body mass index, ESR 1=erythrocyte sedimentation rate in 1 hour, ESR 2=erythrocyte sedimentation rate in 2 hours, CRP=C-Reactive Protein, NLR=neutrophil-to-lymphocyte ratio *= Pearson correlation, #=t Student

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The multivariate regression analysis was assessment at time T1.

We used values for BMI, ESR1, ESR2, CRP, fibrinogen, VAS, Lequesne index, and WOMAC scale, as predictive values for NLR.

However, the analysis did not yield statistically significant results.

Due to this, we performed linear regression for NLR and each of the parameters mentioned earlier.

Statistically significant data was obtained for NLR/ESR1 (p=0.0003) and NLR/ESR2 (p=0.003).

As seen in Figure 2, for each increase in NLR, the value of ESR1 increases by 4.5 (specifically 4.44) points, starting from an initial value of 20 (specifically 19.541).

In Figure 3, the value of ESR2 changes by 7 (specifically 6.71) points, starting from a value of 37 (specifically 36.812), for each increase in NLR.

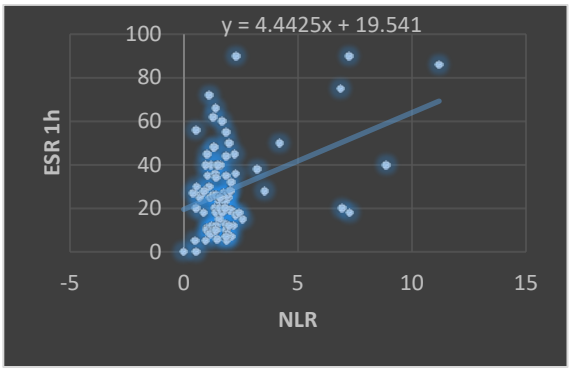

Figure 2. Linear regression ERS1 / NLR.

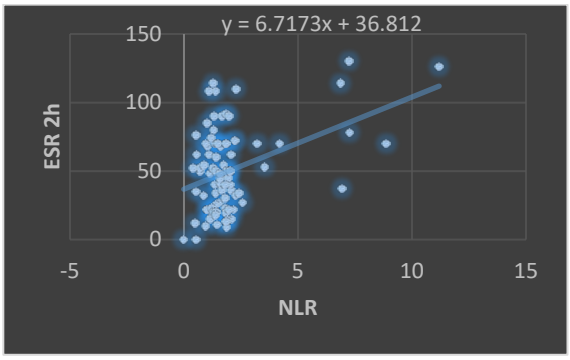

Figure 3. Linear regression ERS2 / NLR.

Discussion

In this study, we described and monitored clinical, paraclinical and functional parameters of KOA patients during functional recovery.

We didn't refer to primary or secondary KOA because in a recent study [25] it was argued that dividing osteoarthritis (OA) into primary and secondary subsets is not useful since "all OA is secondary" and that any attempt to subset OA had to take into account the fact that OA is largely a condition driven by the response to mechanical stress on the joint.

They suggested that sub setting OA should be done on the basis of the mechanical abnormalities.

So, we established BMI, a parameter with significant mechanical impact upon lower limb joints. None patient was normal weight.

The most of them were overweight (34.44%) and obese class I (44.44%), with high value for male patients. It is known that obesity is associated with muscle atrophy relative to body mass, fat infiltration, fibrosis and local inflammation in the quadriceps muscles of rats and a corresponding degeneration of the knee [26].

So, value of BMI can be reflected a painful and disable knee in our patients.

The mean values for BMI in female and male patients have significant correlated (p=0.04, Student test).

The original aspect of our clinical study it represents the role of NLR level in the monitoring the rehabilitation program in KOA patients.

More exactly our patients are included in the second (KOA with associated diseases) sub-phenotype of four sub-phenotypes OA stratification (KOA without any associated diseases, KOA with associated pathology, multi-joint OA without any associated diseases, multi-joint OA with associated pathology) [27].

When we began the study, we took into consideration the conclusions of Sunbul et al. according to which NLR, a blood inflammatory marker obtained through the ratio of neutrophils to lymphocytes, has a better predictive value for inflammation than traditional and single inflammatory markers [28].

NLR is considered an important balance between neutrophils (inflammatory activators) and lymphocytes (inflammatory regulators); a severity of this imbalance is associated with a severity with inflammation process [29].

The mechanism of NLR affecting the KOA may be achieved through significant increase of the inflammatory cytokines [30], IL-6, IL-8, and TNF-α [31].

Inflammatory cytokines can enhance the cellular activity of the synovial tissue, thus neutrophils, platelets, or lymphocytes in peripheral blood significantly increase [32].

So, in the last decade, NLR levels can be used as indicators of systemic inflammation supporting the inflammatory hypothesis of the pathogenesis of osteoarthritis.

KOA had higher NLR compared to healthy people [33,34], and it is associated with severity of this joint disorder but inconsistency about the predictive role of NLR in diagnosis, prognosis or as a marker for disease activity for other diseases.

Our study is prospective study, without a control group, so we couldn't mention a report to healthy people. Similar to literature data, the NLR value in our study didn't correlated with other clinical and functional parameters.

It is important to mention that mean value of blood NLR in T1 moment was ≥2.1 (mean value for all patients was 2.26, with higher mean value for female 3.95 and urban patients 2.59), a cut-off value for predicting severe knee OA [20].

This result has to be interpreted in the context of higher number of patients with moderate (77.77%) and severe (13.33%) KOA.

In their randomised controlled study, Cai et al. mentioned that NLR and microRNA (miR)-141 were significantly increased in the peripheral blood of patients with KOA, and may become a potential therapeutic target osteoarthritis in the future [35].

Our results are consistent with the findings of this conclusion.

Without significant differences between the two evaluation moments, the blood NLR has diminished and it was situated under 2.1 value.

Probably, complete management of KOA patients studied had efficiency in pain and inflammatory joint control.

The mean values of VAS were significant modifying for all patients. In subsidiary, functional status has favourable evolution (mean values of Lequesne index had significant improvement).

Up to 81% of the participants were women, which raises doubts regarding generalizability to men.

Although there was no gender difference between the evolutions of the studied parameters, we noted that blood NLR was higher in T1 for female and the difference after rehabilitation program was greater for women (2.31) compared to men (0.39).

Similarly, the findings of Soysal et. al. [36] there were differences in NLR between patients of different ages, but without statistical significance.

We can explain this because the immune and metabolic functions of older patients decline, and they are more vulnerable to inflammatory responses and diseases.

Almost our studied patients had comorbidities.

This aspect is correlated with other studies, in which it is recorded that NLR represents a significant independent predictor of adverse outcomes in the elderly with diabetes mellitus, hypertension, coronary artery disease, chronic heart failure, ischaemic stroke, peripheral arterial diseases, chronic kidney disease, cancer [37].

Physical function was defined as the ability of a person to move around and to perform types of activity; in the present study we used Lequesne Index and WOMAC scale.

Unlike other studies [38], blood NLR was no correlated with Lequesne Index and WOMAC scores.

This suggests that the two indicators are related to the other conditions of KOA patients and to the complex of rehabilitation measures.

Other factors apart from biological and clinical dimensions can affect the experience of living with knee osteoarthritis [39].

With or without biochemical parameters correlation, physical therapy and kinetic measures decreased pain and improved physical function (strong evidence) and improved health related quality of life (moderate evidence) among people with knee OA.

Measurable benefits of physical activity appeared to persist for periods of up to 6 months following cessation of a defined program [40].

The mean CRP and fibrinogen levels were almost upper normal value.

This result is in accordance with a recent study [41] in which it is specified that high level of CRP was seen in KOA patients with grade 4 of disease.

In our study the most patients had moderate KOA (grade 2 and 3 of disease).

These values of inflammatory parameters (CRP, fibrinogen) permitted to apply the rehabilitation program in our KOA.

In our analysis NLR was not associated with clinical and functional parameters.

We obtained an independent predictor of ERS 1/ERS2 were the only independent predictors of NLR in linear analysis.

So, eternal ERS represents the foundation stone for all lab test and for monitoring the evolution KOA patients.

Current clinical practice guidelines recommend education and self-management, exercise, and weight loss (for over-weight or obese patients) as the first-line treatments for KOA.

These strategies may be the core of KOA rehabilitation, because they have been proven to effectively decrease pain and improve overall joint function and patient quality of life [42].

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Initially, six clinical phenotypes and nine endotypes of KOA have been described [43].

It is important to note that a given OA phenotype may be common to multiple endotypes (subtypes of disease defined functionally and pathologically by a molecular mechanism).

The importance of identifying endotypes for targeted treatment has gained much attention particularly from the point of view of drug discovery, where identifying the right target is key for success [8].

Although NLR is commonly used as an indicator to evaluate the health of patients, and its diagnostic specificity for a certain disease is still poor [44], it may be an instrument for future challenge to identify the clinical phenotypes and clearly define their constituent molecular endotypes in KOA.

Conclusions

Although research in OA has been documented for more than ten decades, further research is needed to clarify strong relationship between inflammatory process, functioning and quality of life in KOA patients.

As an independent diagnostic marker, NLR has limited value but it can be considered an inexpensive additional biomarker for the diagnosis of KOA-one of the major public health.

In the assessment of global KOA patient status (clinical and functional status in accordance with severity of inflammation), NLR has significant value and could be used for monitoring the individualized rehabilitation program.

Conflict of interests

None to declare.

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