Relationship Between Inflammation Parameters Which Are Obtained From Blood Count And Knee Osteophytes

Kan Sayımından Elde Edilen İnflamasyon Parametreleri ve Diz Osteofitleri Arasındaki İlişki

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Abstract

Objective

Osteoarthritis is no longer considered a degenerative disease. The presence of underlying low-grade inflammation has been well demonstrated. Although osteophytes are used to determining the radiological stage, the development mechanism is not fully understood. The aim of this study is to separately evaluate the relationship between various inflammation parameters associated with complete blood count with osteophytes and radiological stage.

Methods:

Patients who met the American College of Rheumatology clinical knee osteoarthritis criteria, retrospectively selected. Kellgren-Lawrence grading scale was used for disease severity and Osteoarthritis research society international grading was used for osteophyte size evolution. Red blood cell distribution width, platelet to lymphocyte ratio, neutrophil to lymphocyte ratio, neutrophil to monocyte ratio, lymphocyte to monocyte ratio, and mean platelet volume obtained from complete blood count, and C-reactive protein levels were recorded. The relationship between inflammation markers and osteophytes and disease stage was evaluated by logistic regression analysis.

Results:

A significant correlation was shown between CRP and PLR in the early stage of the disease. No correlation was found in advanced stage. No correlation was found between osteophyte progression and inflammatory markers in the analysis based on osteophyte size.

Conclusion:

In this study, we have shown that there is a relationship between systemic low-grade markers of inflammation and early stages of knee osteoarthritis, but this relationship was not detected in advanced stages. There was not a relation between osteophyte progression and these markers. Even though it seems to be running together, we can assume that the progression of the disease and osteophyte formation have different mechanisms.

Key Words: Knee Osteoarthritis, Low-grade inflammation, Kellgren-Lawrence grade, Osteophytes, Complete blood count

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ÖZ

Amaç:

Osteoartrit artık sadece dejeneratif bir hastalık olarak kabul edilmemektedir. Altta yatan düşük dereceli inflamasyon varlığı gösterilmiştir. Osteofitler radyolojik evre tespitinde kullanılmasına rağmen gelişim mekanizması tam bilinmemektedir. Bu çalışmanın amacı, tam kan sayımı ile ilişkili çeşitli inflamasyon parametrelerinin osteofitler ve radyolojik evre ile ilişkisinin ayrı ayrı değerlendirilmesidir.

Metot:

Klinik olarak ACR (American Collage of Rheumatology) diz osteoartriti kriterlerini karşılayan hastalar, geriye dönük olarak seçilmiştir. Kellgren-Lawrence derecelendirme ölçeği hastalık şiddeti için, OARSI (Osteoarthritis research society international grading) sınıflaması ise osteofit boyutunun değerlendirilmesi için kullanıldı.Tam kan sayımından elde edilen kırmızı kan hücresi dağılım genişliği (RDW), trombosit/lenfosit oranı (PLR), nötrofil/lenfosit oranı (NLR), nötrofil/monosit oranı (NMR), lenfosit/monosit oranı (LMR), ortalama trombosit hacmi (MPV) ve C-reaktif protein (CRP) seviyeleri kaydedildi. İnflamasyon belirteçleri ile osteofitler ve hastalık evresi arasındaki ilişki lojistik regresyon analizi ile değerlendirildi.

Bulgular:

CRP ve PLR ile hastalığın erken döneminde anlamlı bir korelasyon gösterildi. İleri evre hastalıkta ise herhangi bir korelasyon saptanmadı. Osteofit büyüklüğüne göre bakılan analizde ise osteofit progresyonu ile inflamatuar belirteçler arasında bir korelasyon gösterilememiştir.

Sonuçlar:

Sonuçlarımıza göre, sistemik düşük dereceli inflamasyon belirteçleri ile diz osteoartritinin erken evrelerinde bir ilişki olduğu gösterilmiş olup bu ilişki ileri evrelerde saptanmamıştır. Osteofit progresyonu ile bu belirteçler arasında bir ilişki gösterilememiştir. Her ne kadar birlikte seyrediyor gibi olsa dahi hastalığın ilerlemesi ve osteofit oluşumunun farklı mekanizmalara sahip olduğunu varsayabiliriz.

Anahtar Kelimeler: Diz Osteoartriti, Düşük dereceli inflamasyon, Kellgren-Lawrence evrelemesi, Osteofitler, Tam kan sayımı

INTRODUCTION

Osteophytes are one of the major features of knee osteoarthritis (OA) and associated with pain and disability (1). Osteophytes can be seen in every stage of knee OA and even prior to the joint space narrowing. Periosteal or synovial mesenchymal cells are showed to be the cellular origin of osteophytes. The trigger mechanism is still unclear whether functional adaptation to any structural changes or an abnormal remodeling process originated from periosteum or synovia (2). There is no single mechanism to explain the presence of osteophytes.

Our knowledge about the underlying subclinical/ low-grade inflammation in OA is growing (3, 4). İmaging studies and histological analysis revealed that synovial inflammation accompanies in all stages of OA (5) and Wojdasiewicz et al described the dominance of inflammatory cytokines in the pathogenesis (6). The complete blood count (CBC) parameters related markers, like RDW (Red blood cell distribution width), PLR (platelet to lymphocyte ratio), NLR (neutrophil to lymphocyte ratio), NMR (neutrophil to monocyte ratio), LMR(lymphocyte to monocyte ratio), MPV(mean platelet volume), etc are recently investigated popular markers in most inflammatory conditions and OA. Most of the studies in this field focus only on Kellgren-Lawrence (KL) grading or joint space narrowing alone to determine disease activity (7-12). Joint space narrowing and osteophyte, which are major findings, do not always have to be synchronized (13). It is important to evaluate these features separately to find out the disease progression. Only a few studies provide separate information on osteophytes (14-16). Among the inflammatory markers obtained from CBC, only one study found that evaluating osteophytes alone rather than the Kelgren-Lawrence grading and reported that increasing RDW levels were associated with the increased risk of osteophytes (17). This finding provides additional support for the possible inflammatory process underlying osteophyte formation (OF) but not enough alone. This study aimed to evaluate the relationship between knee osteophytes and the low-grade inflammation using peripheral blood count related parameters.

METHODS

The study was carried out according to the ethical standards specified in the 1964 Helsinki Declaration. In our study, research and publication ethics were complied. Ethics committee approval was obtained from the Cukurova University non-invasive clinical research ethics committee with the number 96 on February 14, 2020. Patients classified as knee osteoarthritis according to the ACR (American College of Rheumatology) criteria (18) above 18 years of age who applied to our clinic between January 2019 and January 2020 were retrospectively scanned. Exclusion criteria are defined as iron deficiency anemia, thalassemia, blood transfusion history, history of rheumatic disease, diabetes, malignancy, pregnancy, previous knee surgery history, synovial tumor (chondroma, etc) and presence of infection. Age, gender, height, weight and body mass index (BMI) were recorded.

Radiologic evolution was based on plain radiographs, standing anteroposterior view (full extension) of both knees. Kellgren-Lawrence grading scale was used for disease severity and OARSI (Osteoarthritis research society international) grading was used for osteophyte size evolution. Although both knees were graded the highest grade was chosen for the patient's final KL grade and OARSI grade.

Kellgren-Lawrence Grading Scale: Grade 0: no x-ray changes, Grade 1: doubtful narrowing of joint space and possible osteophyte lipping, Grade 2: definite osteophytes, definite narrowing of joint space, Grade 3: moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone contour, Grade 4: large osteo-

phytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour (19).

Using this radiologic scale, we defined 3 groups of the patients to refer to the disease severity: group1: Kellgren-Lawrence 1 (nonspecific radiologic findings), group 2: Kellgren-Lawrence 2 (mild Knee OA) and group 3: Kellgren-Lawrence 3 and 4 (moderate-severe knee OA).

OARSI grading for osteophytes: Grade 0: normal, Grade 1: minimal change, Grade 2: moderate change, Grade 3: severe change (20).

According to the OARSI Grading scale, we defined 3 groups of the patients to refer to osteophyte size: group 1: OARSI grade 0 (non-osteophyte), group 2: OARSI 1 (small osteophytes) group 3: OARSI 2 and OARSI 3 (medium-large osteophytes)

Laboratory evolution: CBC related parameters; RDW, PLR, NLR, NMR, LMR, MPV, and CRP(C-reactive protein) levels were recorded.

Statistical analysis: Statistical analyzes were made using SPSS-18. Average and standard deviation were calculated in the descriptive analysis of numerical variables. The number and percentage were calculated in the descriptive analysis of categorical variables. The suitability of variables to normal distribution was evaluated by visual (histogram) and analytical (Kolmogorov –Smirnov/ Shapiro-Wilk) methods. When the difference of numerical variables among multiple independent groups is examined, one-way analysis of variance (ANOVA) if normal distribution, and Kruskal-Wallis test was performed if it does not fit the normal distribution. The relationship between two non-normally distributed numerical variables was evaluated by the Spearman correlation. Factors that may affect the severity of disease categorized by Kellgren-Lawrence were subjected to univariate logistic regression analysis, respectively. Statistically significant factors (P <0.05) were included as independent variables in the multinominal logistic regression analysis model. Factors that may affect the size of osteophyte categorized by OARSI were subjected to univariate logistic regression analysis, respectively. Statistically significant factors (p <0.05) were included as independent variables in the multinominal logistic regression analysis model. We reduced the model using the enter method. P value <0.05 was considered statistically significant and the confidence interval was %95.

RESULTS

Initially, 317 patients met the ACR knee OA criteria. 27 patients were excluded due to the lack of medical records. 162 patients (84.7% female; mean age 52.67 ± 11.26 years) were enrolled finally after the exclusion criteria were applied. Applied exclusions were listed as; iron deficiency anemia (n=37), thalassemia (n=5), blood transfusion history, history of rheumatic disease (n=13), diabetes (n=42), malignancy, pregnancy, previous knee surgery history (n=23), synovial tumor (chondroma, etc) (n=3), and presence of infection (n=5). According to the Kellgren-Lawrence grading 70 patients were classified as mild knee OA(KL 2) and 52 patients were classified as moderate-severe knee OA(KL3+KL4). 40 Patients had non-specific radiological findings (KL 1). Demographics and the clinical characteristics of the patients were presented in Table 1. Age, BMI, PLR, NMR, and LMR were statistically different between groups according to KL grading (Table I).

Table I Demographic and clinical characteristics and laboratory parameters of patients according to osteoarthritis severity.

	Non-spesific Radiologic Findings (n= 40)	Mild Knee OA (n=70)	Moderate-severe Knee OA(n=52)	P value
Sex n (%) Female Male	32(%80) 8(%20)	52(%74.3) 18(%25.7)	42(%80.8) 10(%19.2)	0.645
Age (years) mean±SD	55.35±11.35	60.30±10.319	65.63±10.581	*0.00*
Height (m) mean±SD	1.686±.0793	1.69±.095	1.67±.08	0.197
Weight (kg) mean±SD	72.75±10.112	75.84±10.668	81.15±12.19	0.385
BMI (kg/m^2). mean±SD	25.633±3.566	26.561±4.210	29.33±5.653	*0.014*
CRP (mg/L) mean±SD	3.88±4.657	7.221±11.805	6.006±5.635	0.157
PLR mean±SD	121.888±26.304	109.658±34.413	131.575±41.839	*0.035*
NLR mean±SD	2.458±2.608	2.081±1.924	2.408±1.098	0.07
NMR mean±SD	10.567±12.242	8.032±2.666	8.369±3.479	*0.01*
LMR mean±SD	4.326±1.691	4.5160±1.481	3.816±1.514	*0.004*
RDW (%) mean±SD	13.387±.840	13.43±1.169	13.548±1.006	0.207
MPV (fL) mean±SD	10.13±.797	11.151±8.715	10.455±1.01	0.248

OA; Osteoarthritis, BMI; Body Mass Index, CRP; C-Reactive Protein, PLR; Platelet-lymphocyte ratio, NLR; Neutrophil-lymphosit ratio,
NMR; Neutrphil-Monocyte Ratio, LMR; Lymphocyte-monocyte ratio, RDW; Red Blood Cell Width, MPV; Mean Platelet Volume

According to the OARSI criteria, 57 patients had no definite osteophyte, 45 patients had small osteophytes and 60 patients had medium-large size osteophytes. While age (p=0.003), weight (p=0.003), and BMI (p<0.01) were statistically significantly different between these groups, the other parameters were not (Table II).

Table II Demographic and clinical characteristics and laboratory parameters of patients according to osteophyte size

	No osteophyte (n= 57)	Small osteophytes (n=45)	Medium-large osteophytes (n=60)	P value
Sex n (%) Female Male	45(%78.94) 12(%21.06)	33(%73.3) 12(%26.7)	48(%80) 12(%20)	0.694
Age (years) mean±SD	57.60±10.972	59.93±12.743	64.47±9.38	*0.003*
Height (m) mean±SD	1.693±.0.820	1.692±0.994	1.67±.081	0.3
Weight (kg) mean±SD	73.81±11.725	75.40±10.478	80.65±10.976	*0.003*
BMI (kg/m^2). mean±SD	25.853±4.476	26.397±3.635	29.145±5.288	*0.00*
CRP (mg/L) mean±SD	5.563±7.859	7.044±12.765	5.64±5.31	0.648
PLR mean±SD	119.65±34.87	112.83±36.40	124.93±37.36	0.242
NLR mean±SD	2.56±2.92	1.88±0.78	2.30±1.07	0.206
NMR mean±SD	9.76±10.43	7.86±2.27	8.48±3.45	0.332
LMR mean±SD	4.27±1.76	4.51±1.47	4.01±1.41	0.261
RDW (%) mean±SD	13.36±0.952	13.51±1.23	13.49±0.969	0.723
MPV (fL) mean±SD	10.14±0.967	11.63±10.85	10.46±0.926	0.406

OA; Osteoarthritis, BMI; Body Mass Index, CRP; C-Reactive Protein, PLR; Platelet-lymphocyte ratio, NLR; Neutrophil-lymphosit ratio,
NMR; Neutrphil-Monocyte Ratio, LMR; Lymphocyte-monocyte ratio, RDW; Red Blood Cell Width, MPV; Mean Platelet Volume

Univariate analysis for disease severity and osteophyte size was completed one by one with the variables age, BMI, CRP, RDW, MPV, PLR, NLR, NMR, and LMR. Age, BMI, CRP, and PLR had a significant relation with disease activity. Only age and BMI had a significant relation with osteophyte formation (Table III).

Table III Results of univariate analysis between clinical blood parameters and disease severity and osteophyte size groups

Effect	Disease Severity (Kellgren-Lawrence)				Osteophyte size(OARSI)			
	Model Fitting Criteria	Likelihood Ratio Tests			Model Fitting Criteria	Likelihood Ratio Tests		
	-2 Log Likelihood of Reduced Model	Chi-Square	df	Sig.	-2 Log Likelihood of Reduced Model	Chi-Square	df	Sig.
Age	197.005	20.352	2	*.000*	198.530	11.696	2	*.003*
BMI (kg/m^2).	322.128	16.047	2	*.000*	327.317	15.920	2	*.000*
CRP (mg/L)	312.424	6.402	2	*.041*	315.651	.805	2	.669
RDW (%)	167.595	.622	2	.733	172.168	.671	2	.715
MPV (fL)	176.921	1.546	2	.462	178.218	2.309	2	.315
PLR	345.355	11.573	2	*.003*	353.552	2.939	2	.230
NLR	346.166	1.524	2	.467	352.166	5.110	2	.078
NMR	344.780	3.544	2	.170	349.394	2.514	2	.285
LMR	344.780	6.767	2	*.034*	350.780	2.762	2	.251

The null hypothesis is that all parameters of that effect are 0.
OA; Osteoarthritis, BMI; Body Mass Index, CRP; C-Reactive Protein, PLR; Platelet-lymphocyte ratio, NLR; Neutrophil-lymphosit ratio, NMR; Neutrphil-Monocyte Ratio, LMR; Lymphocyte-monocyte ratio, RDW; Red Blood Cell Width, MPV; Mean Platelet Volume

Multivariate logistic regression analysis was completed with the variables age, BMI, CRP, PLR, and LMR for disease severity. The null hypothesis was based on group 1(nonspecific radiologic findings). The final model revealed that age, BMI, CRP, and PLR were statistically significant predictors. (p=0.00, p=0.001, p=0,012 and p=0.012 respectively). Parameter estimates revealed that Mild knee OA can be predicted by age, CRP, and PLR, but not BMI. Moderate-severe knee OA can be predicted by age and BMI only (Table IV).

Table IV Variables associated with disease severity by multivariate analysis

Disease severity (a)		Wald	P value	OR (%95CI)
Mild knee OA				
	Age	4.940	*.026*	1.045 (1.005-1.087)
	BMI (kg/m^2).	.184	.668	1.023 (.923-1.133)
	CRP (mg/L)	5.548	*.019*	1.141(1.022-1.273)
	PLR	4.033	*.045*	.986 (.973-1.000)
	LMR	.018	.894	1.019(.775-1.338)
Moderate- severe knee OA				
	Age	13.746	*.000*	1.090(1.041-1.141)
	BMI (kg/m^2).	8.634	*.003*	1.175(1.055-1.308)
	CRP (mg/L)	3.003	.083	1.105(.987-1.238)
	PLR	.256	.613	1.004(.989-1.018)
	LMR	.582	.446	.876(.622-1.232)

a The reference category is: Non-spesific radiologic findings(KL1)
OR; Odds Ratio, CI; Confidence Interval, OA; Osteoarthritis, BMI; Body Mass Index, , CRP; C-Reactive Protein, PLR; Platelet-lymphocyte ratio, LMR; Lymphocyte-Monocyte Ratio

Multivariate logistic regression analysis was completed with the variables age and BMI for osteophyte size. The null hypothesis was based on the none-osteophyte group. The final model revealed that age (P=0.008) and BMI (p= 0.001) were statistically significant predictors. Parameter estimates revealed that small osteophytes can be predicted by neither age (p=0.343) nor BMI (p=0.607), while medium-large osteophytes can be predicted by both (p=0.03 and p<0.01 respectively) (Table V).

Table V Variables associated with osteophyte size by multivariate analysis

Osteophyte size (a)		Wald	P value	OR (%95 CI)
Small				
	Age	.900	.343	1.017 (.982-1.054)
	BMI (kg/m^2).	.264	.607	1.026 (.931-1.129)
Medium large				
	Age	8.681	*.003*	1.058 (1.019-1.098)
	BMI (kg/m^2).	10.397	*.001*	1.158 (1.059-1.266)

a The reference category is: none-osteophyte
OR; Odds Ratio, CI; Confidence Interval, BMI; Body Mass Index

DISCUSSION:

In this paper, we showed that there was an association between inflammatory markers PLR and CRP, in the early stages of knee osteoarthritis but not the later stages. In the later stages, only age and BMI were predictive. The second finding was, although it was part of KL staging, we could not show any relationship between osteophyte formation and inflammatory markers neither early nor late stages. Age and BMI were predictive only for large osteophyte formations, not the small ones.

Beside complex inflammation markers, simple or easily accessible inflammation markers are also being investigated in the scientific area (7, 8). We designed our study with easy accessible inflammatory markers (CRP, PLR, NLR, NMR, LMR, MPV, and RDW) which are investigated in patients with OA. Researchers revealed that most of these markers also related to the radiologic severity (10-12, 21, 22). Our results were partially consistent with the previous findings that we are only able to show the relevance of CRP and PLR. Additionally, this relation was available only in the early stages. BMI and age were also contributing factors only in the later stages.

It is well known low-grade inflammation accompanies osteoarthritis either local or systemically (3). However, the role of low-grade inflammation in the pathogenesis of osteoarthritis is still not clear. Where does the process start: cartilage or bone? In the early stages or during the whole process? How can one be associated with mechanical factors? There are too many questions required to answer. We can speculate with our results that systemic low-grade inflammation is important even in the onset of the disease. Previously,

significantly elevated CRP levels were found in early knee OA and a meta-analysis revealed that high CRP levels were not associated with radiologic disease severity (23-25). Additionally, PLR had a significant association with early disease activity in our study. Formerly, in patients with knee OA, increased PLR was determined, without any association with disease severity (12). Association between the disease severity and PLR has been shown in hip OA previously (26). As far as our knowledge, this paper is the first that showed significant association with PLR and early stages of knee OA. With CRP and PLR relations in the early stages, we might assume that disease onset more related to systemic low-grade inflammation.

Kellgren-Lawrence is a radiologic grading established for knee osteoarthritis (19). Joint space narrowing provides indirect information about the cartilage damage and is used in KL staging as a major feature (27). Another major feature is osteophytes. Marginal osteophytes are commonly present in knee OA (28). Although major features, joint space narrowing (JSN) and osteophyte formation (OF) are evaluated together in the staging, they are not necessarily synchronized always. Boegard et al showed a significant decrease in joint width in the medial compartment of the knee, in 2 years, even with the knees without osteophyte (13). In contrast to osteophyte formation, JSN has been associated with disease severity more and explains OA progression better in studies (13, 29-31). Oka et al did not identify a correlation between JSN and OF (32). Another study revealed that correlation becomes apparent only in the later stages (30). Probably there are different mechanisms to explain each one.

If they are not synchronized always what comes first in the process? Osteophytes or joint space narrowing? In the developing process of OA, the formation of osteophytes is likely an adaptive response to other structural changes and correlated with cartilage damage and malalignment (31, 33). The osteophyte area has been related to the cartilage degeneration markers (COMP) but not the JSN (15). İnflammation seems also affects the cartilage and a vicious cycle starts between inflammation and degeneration (34). The occurrence of osteophytes might not be related to the onset of the disease even if it is associated with the cartilage damage (30).

Trigger factors for the OF are still unknown. Mechanical factors like load, trauma, and malalignment are investigated factors (31, 35). The protection of the paralytic or immobile joints from the osteoarthritic changes emphasizes the importance of the mechanical stimulus (36). The rat model also confirms mechanical stimulation triggers the OF (37). Excessive load seems to have potential by causing cartilage loss and also affects the bone structure beneath the cartilage (38). On the other hand low-grade inflammation enhanced by the adipokines, turn to overweight a more complex source in the pathogenesis (39, 40). Van der Kraan et al reviewed that TGF B (Transforming Growth Factor Beta) and growth factors originated from the murine synovial macrophages are potential biochemical triggers of OF (2). As a summary, chronic mechanical impairment in combination with metabolic dysregulation seems a common trigger of subchondral bone changes and osteophytosis (41).

Studies mostly support local inflammation and mechanical impairment in the development of osteophytes (42, 43). Human studies revealed that synovial fluid macrophage originated inflammation markers (MMP-3, VEGF, and TIMP-1), but not the plasma, is associated with OF and OA severity (43). Effusion-synovitis is a clinical reflection of local inflammation and its relation with osteophytes relation has controversy in the literature. Wang et al showed that effusion synovitis did not predict any structural changes including osteophytes (44). However, Yang et al reported that effusion-synovitis was associated not only with osteophytes, and joint space narrowing and Kellgren Lawrence grade (16). Due to the highly vascularized nature of synovial tissue, systemic inflammation will have an expected reflection on the synovia (41). There is less evidence about the influence of systemic inflammation on osteophytes. In a fat transgenic mice model, CRP was found responsible for the aggravation of OF independently (23). As the opposite view, the study by Van Spil et al, serum ESR levels were found negatively associated with OF (15). Among the CBC related inflammation parameters, Wu Z. et al referred specifically to RDW as a systemic inflammatory marker for osteophytes (17). In our study, besides RDW, we are far from supporting low-grade systemic inflammation with CRP or any of the parameters from the CBC, for osteophytes in particular. Local inflammation might be more responsible for OF rather than systemic (42).

A study by Demirağ et al showed that obesity had a stronger association with an OF rather than JSN (45). Leptin seems suspected as the key molecule in the progression of osteophytes (2) and current literature supports the local inflammatory-related role rather than mechanical load in the pathogenesis (40, 46). We found that BMI was predictive for both larger osteophytes and the later stages of the disease. We can assume that overweight can contribute to progression of existing osteophyte. Our results were consistent with the previous results.

In this paper, we explored the relationship between blood parameters and disease severity, osteophyte formation in OA patients. To our knowledge, this is the first study to show a significant association with PLR and early disease activity in knee OA. To investigate CBC related inflammatory parameters with knee OA we evaluate KL grade and OARSI grade together and found different relations for each. Nevertheless, our study has some limitations. Firstly this study was designed as retrospective. We did not include any joint biomechanics to assess mechanical factors properly. We could not evaluate any clinical scale. In order to generalize our results, it is necessary to work with larger patient groups.

Conclusion: Different mechanisms seem to be responsible for different stages of the disease. Discovering the exact pathogenesis provides us targeted treatment options. It is obvious that this field requires more studies.

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