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Association of Hemogram Parameters with Body Mass Index in Knee Osteoarthritis

Diz Osteoartritinde Hemogram Parametrelerinin Vücut Kitle İndeksi ile İlişkisi

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ABSTRACT

Objective: This study aims to investigate the relationship between hemogram parameters, which are low-cost, easy, routinely applied low-grade inflammation indicators, and severity of knee osteoarthritis (KOA) and obesity.

Materials and Methods: This study involved 140 KOA patients aged 45 to 85 who underwent knee radiographs, weight and height measurements, and routine laboratory tests. Recorded data included demographic information (gender, age), body mass index (BMI), routine hemogram, and laboratory parameters. Patients were categorized into two groups based on their Kellgren-Lawrence (KL) scores (mild: KL 1-3, severe: KL 4) and four groups according to their BMI (BMI <25, BMI = 25-30, BMI = 30-35, BMI >35).

Results: The findings revealed significantly elevated levels of serum Neutrophil-to-Lymphocyte Ratio (NLR) and C-reactive protein (CRP) in severe KOA compared to mild KOA (P<0.05). Evaluation by BMI demonstrated a statistically significant increase in serum NLR and Neutrophil-to-monocyte Ratio (NMR) in patients with BMI>30 in mild KOA groups, while mean blood NLR was notably higher in patients with BMI=30-35 in severe KOA groups.

Conclusions: These results suggest that NLR and NMR could provide a new perspective on the relationship between obesity and mild KOA in clinical practice, presenting a cost-effective and easily applicable alternative for determining disease prognosis and progression.

Keywords: Knee osteoarthritis, neutrophil/lymphocyte ratio, neutrophil monocyte ratio

ÖZ

Amaç: Bu çalışmada, düşük maliyetli, kolay, rutin olarak uygulanan düşük dereceli inflamasyon göstergeleri olan hemogram parametreleri ile obezite ve diz osteoartriti (DOA) şiddeti arasındaki ilişkinin araştırılması amaçlanmıştır.

Materyal ve Metot: Bu çalışmaya, diz grafileri, kilo ve boy ölçümleri ve rutin laboratuvar testleri yapılmış 45-85 yaş arası 140 KOA hastası dahil edilmiştir. Kaydedilen veriler demografik bilgileri (cinsiyet, yaş), vücut kitle indeksini (BMI), rutin hemogramı ve laboratuvar parametrelerini içeriyordu. Hastalar Kellgren-Lawrence (KL) skorlarına göre iki gruba (hafif: KL 1-3, şiddetli: KL 4) ve BMI'larına göre dört gruba (BMI<25, BMI=25-30, BMI=30-35, BMI>35) ayrılmıştır.

Bulgular: Bu çalışmada, serum CRP ve NLR değerleri şiddetli DOA hastalarında hafif DOA hastalarına kıyasla anlamlı derecede yüksek bulunmuştur (P<0,05). VKİ'ye göre değerlendirildiğinde, kan nötrofil lenfosit (NLR) ve nötrofil monosit (NMR) oranları hafif DOA gruplarında VKİ>30 olan hastalarda istatistiksel olarak anlamlı şekilde artmıştır. Ayrıca, şiddetli DOA gruplarında ortalama kan NLR değeri VKİ=30-35 olan hastalarda diğer gruplara kıyasla anlamlı derecede yüksek bulunmuştur.

Sonuç: Bu sonuçlar, NLR ve NMR'nin klinik ortamda obezite ve hafif DOA arasındaki ilişkiye yeni bir bakış açısı sağlayabileceğini göstermektedir. Bu parametrelerin düşük maliyetli ve kolay uygulanabilmesi, hastalığın prognozunu ve seyrini belirlemede alternatif olabilir.

Anahtar Kelimeler: Diz osteoartriti, nötrofil/lenfosit oranı, nötrofil/monosit oranı

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INTRODUCTION

Osteoarthritis (OA) is a complex, chronic, degenerative joint disease characterized by the destruction of articular cartilage and disruption of normal bone formation and breakdown processes. Knee osteoarthritis (KOA) is the most prevalent form of OA.[1] OA develops by combining processes within the subchondral bone, including erosion, sclerosis, osteophytes, subchondral cysts, and synovial inflammation. However, the pathophysiology of OA is still poorly understood.[2]

The main risk factors for KOA are age, obesity, gender, and inflammation.[3] According to the World Health Organization (WHO), obesity is the abnormal or excessive accumulation of fat associated with poor health. According to this calculation, a body mass index (BMI) greater than 30 is considered obese.[4] Physical inactivity, poor eating habits, and genetic factors are commonly associated with obesity.[5] Recently, obesity has been recognized as a major risk factor for KOA and is considered a low-grade inflammatory disease.[6] Abnormal mechanical loading of joints in obesity leads to changes in the composition of the cartilage matrix and joint degeneration, impacting joint biomechanics.[7] However, recent epidemiological data suggest that obese people have about twice the risk of hand OA as normal-weight people, suggesting a more complex relationship.[8] The assessment of KOA is usually based on clinical and radiological findings. The most commonly used radiographic measure of disease severity is the Kellgren-Lawrence (KL) grade.[9] In recent years, as the disease can be diagnosed by pathological findings, new biomarkers and parameters have been emphasized for disease diagnosis and treatment.[10]

OA was considered a noninflammatory disease. However, recent studies have shown that inflammation is a risk factor for both progressive cartilage destruction and symptoms, including joint pain, palpable joint swelling, synovial edema, and osteoarthritis.[11] Complete blood count (CBC) analyses, known for their cost-effectiveness and rapid results, play a crucial role in assessing various diseases. Hemogram parameters such as the platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio (NLR), and neutrophil/monocyte ratio (NMR), along with biochemical markers like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), have emerged as systemic inflammation indicators across various diseases.[12-16]

Inflammation is an important risk factor for both OA and obesity. Therefore, the purpose of this retrospective study is to determine the relationship between hemogram and biochemical parameters, which are low-cost, easy, routinely applied low-grade inflammation indicators, and severity of disease and obesity, as an alternative to showing the prognosis and course of the disease.

MATERIALS AND METHODS

Ethical Considerations: This study was approved by the Ethics Committee of the Medical Faculty of Atatürk University (Date: 30.11.2017, decision no: B.30.2.ATA.0.01.00/91). The study was conducted in accordance with the Helsinki Declaration of 1975, which was revised in 2000.

Participants: For the study, the KOA patients who had been evaluated between August 2016 and December 2017 in the orthopedics and traumatology polyclinic of Erzurum Regional Training and Research Hospital were retrospectively screened by the orthopedic traumatologist. All patients were diagnosed with KOA using the American College of Rheumatology clinical criteria.[17] Patients with autoimmune disorders, post-infectious or post-traumatic arthropathies, systemic inflammation or infection, active malignancy, cardiovascular disease, renal disease, chronic liver disease, and a history of blood transfusion within the previous three months were excluded from the study. According to the hospital software records, 200 patients with KOA diagnosis were screened. One hundred forty patients with knee x-rays, age 45-85 years, weight and height measurements and routine laboratory examinations were included in the study. Demographic data (gender, age) and BMI of KOA patients were determined. Knee radiographs were taken and radiologically graded according to the KL scoring system.[9] This score is based on four radiographic characteristics: joint space narrowing, osteophytes, subchondral cysts, and subchondral sclerosis. Patients were divided into two groups by KL grade: patients with KL grade 1-3 (mild) and patients with KL grade 4 (severe). The patients were also divided into four groups according to BMI: patients with BMI > 35, patients with BMI = 30-35, patients with BMI = 25-30 and patients with BMI < 25.

Laboratory: The laboratory results of the patients were examined. ESR and CRP were obtained from biochemical analyses. White blood cell (WBC), lymphocyte, neutrophil, thrombocyte, and monocyte counts were obtained from the hemogram. Blood NLR, PLR, and NMR levels were calculated. NLR was calculated by dividing neutrophil count by lymphocyte count, PLR by thrombocyte count by lymphocyte count and NMR by neutrophil count by monocyte count. Laboratory and radiological evaluation data were obtained from the same patient.

Statistical Analysis: All statistical analyses were performed using SPSS software version 20. Results were presented as mean±standard deviations for age,

BMI, hemogram and biochemical parameters. Statistical comparison of laboratory parameters levels from mild and severe KOA was used in Independent -Samples T tests. According to BMI, statistical comparison of laboratory parameters levels of groups was used the Kruskal Wallis test and Pairwise comparisons were performed using the Mann-Whitney U test. Statistical significance was defined as a P value < 0.05.

RESULTS

A retrospective analysis encompassed 140 patients stratified into two groups based on the severity of KOA: mild KOA and severe KOA. The comparative assessment of demographic and laboratory parameters, as illustrated in Table 1, revealed noteworthy distinctions between the two groups. Patients with severe KOA exhibited significantly higher mean age (P=0.001), mean CRP (P=0.009), mean neutrophil count (P=0.044), and mean blood NLR (P=0.036) compared to those with mild OA. However, the observed variations in mean ESR, mean WBC, mean PLR and mean NMR did not reach statistical significance. These findings underscore the relevance of age, CRP levels, neutrophil count, and blood NLR in distinguishing the severity of KOA within the studied patient cohort (Table 1).

A cohort of 50 patients diagnosed with mild KOA underwent a comprehensive evaluation, with particular attention given to BMI categorization. The patients were grouped into four BMI categories: BMI<25, BMI=25-30, BMI=30-35, and BMI>35. The comparative analysis of demographic and laboratory parameters across these BMI groups is detailed in Table 2. Notably, patients with BMI=30-35 and BMI>35 exhibited a significant increase in mean blood NLR compared to those with BMI=25-30. Similarly, mean blood NMR showed a noteworthy elevation in patients with BMI=30-35 and BMI>35 compared to those with BMI<25 and BMI=25-30. However, other parameters did not display statistically significant differences among the four BMI groups (Table 2).

Table 1. Comparison of mild and severe KOA in terms of demographics and laboratory parameters.

Parameters	Mild KOA (n=50)	Severe KOA (n=90)	p[a]
Age	60.840 ± 7.527	65.511 ± 7.527	0.001*
BMI	32.019 ± 8.956	31.344 ± 5.371	0.497
WBC	7.478 ± 1.871	8.226 ± 2.576	0.073
CRP, (mg/dL)	0.506 ± 0.531	1.983 ± 3.893	0.009*
ESR, (mm/h)	13.220 ± 8.330	16.766 ± 12.257	0.070
Neutrophil count, (K/uL)	4.678 ± 1.541	5.377 ± 2.143	0.044*
Lymphocyte count, (K/uL)	2.359 ± 0.712	2.191 ± 0.806	0.221
Thrombocyte count, (K/uL)	300.41 ± 87.968	289.233 ± 86.760	0.493
Monocyte count, (K /uL)	0.498 ± 0.165	0.522 ± 0.207	0.469
NLR	2.222 ± 1.291	2.777 ± 1.578	0.036*
PLR	137.480 ± 58.822	146.362 ± 71.385	0.455
NMR	10.134 ± 4.370	11.025 ± 4.668	0.271

Results are given in mean ±SD; [a]: Independent-Samples T tests; *:P-value of <0.05 was considered to be significant; BMI: body mass index; WBC: White blood cell; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NLR:neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; NMR: neutrophil/monocyte ratio.

Table 2. According to BMI, comparing demographic and laboratory parameters in mild KOA.

Parameters	Mild KOA (n=50)				
	BMI <25	BMI =25-30	BMI =30-35	BMI >35	p[a]
Age	62.7±10.9	58.7±8.3	61.3±9.8	61.5±8.4	0.895
WBC	7.5±1.02	7.4±1.4	7.1±2.4	7.6±2.1	0.277
CRP, (mg/dL)	0.36±0.05	0.36±0.09	0.55±0.38	0.65±0.8	0.110
ESR, (mm/h)	9.7±5.5	13.4±10.2	15.6±7.5	13.3±8.0	0.588
Neutrophil count, (K/uL)	4.62±1.27	4.12±1.02	4.46±2.13	5.27±1.5	0.165
Lymphocyte count, (K/uL)	2.3±0.76	2.76±0.68	2±0.47	2.21±0.7	**0.027**[*4,5]
Thrombocyte count, (K/uL)	313±79	316±60	245±34	308±119	**0.023**[*2,4]
Monocyte count, (K/uL)	0.59±0.13	0.55±0.16	0.39±0.08	0.46±0.1	**0.014**[*2,3,4]
NLR	2.32±1.31	1.57±0.57	2.59±2.27	2.52±0.9	**0.027**[*4,5]
PLR	151±63	119±31	129±42	150±77	0.422
NMR	8.21±4.37	7.85±2.36	11.7±6.22	12.07±4	**0.002**[*2,3,4,5]

Results are given in mean ±SD; [a]: The Kruskal-Wallis test was used for the comparison of the groups; For pairwise comparisons, the Mann-Whitney U test was used; *: P value of <0.05 was considered significant; Pairwise comparisons of groups [1]: BMI <25 vs BMI 25-30; [2]BMI <25 vs BMI 30-35; [3]: BMI <25 vs BMI >35; [4]: BMI 25-30 vs BMI 30-35; [5]: BMI 25-30 vs BMI>35; [6]: BMI 30-35 vs BMI>35; BMI: body mass index; WBC: White blood cell; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NLR:neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; NMR: neutrophil/monocyte ratio.

Concurrently, a cohort of 90 patients diagnosed with severe KOA underwent a parallel evaluation, with BMI stratification into four groups: BMI <25, BMI = 25-30, BMI = 30-35, and BMI >35. The comparative analysis of demographic and laboratory parameters across these BMI groups is presented in Table 3. A statistically significant difference was observed in mean age across all four BMI groups. Additionally, mean blood NLR exhibited a significant increase in patients with BMI =30-35 compared to other groups, and a similar tendency was noted for patients with BMI >35 compared to those with BMI < 25. However, no statistically significant differences were identified among the four groups for other parameters (Table 3).

Table 3. According to BMI, comparing demographic and laboratory parameters in severe KOA.

Parameters	Severe Knee OA (n=90)				
	BMI <25	**BMI =25-30**	**BMI =30-35**	**BMI >35**	**p[a]**
Age	70.6±7.1	68.1±5.5	62.6±7.4	63.5±7.6	**0.002**[*2,3,4,5]
WBC	7.8±2.03	8.1±2.7	8.2±2.7	8.5±2.5	0.938
CRP, (mg/dL)	1.04±1.1	2.24±4.1	2.24±4.8	1.8±2.8	0.727
ESR, (mm/h)	14±11.4	16±10.8	17.2±14	18±11.9	0.706
Neutrophil count, (K/uL)	5.1±2.08	5.56±2.3	5.95±2.1	6.01±1.8	0.186
Lymphocyte count, (K/uL)	1.96±0.8	1.98±0.8	2.48±0.7	2.11±0.6	**0.021**[*2,4]
Thrombocyte count, (K/uL)	293±106	264±76	295±87	380±82	0.353
Monocyte count, (K/uL)	0.46±0.1	0.51±0.2	0.52±0.2	0.56±0.1	0.147
NLR	3.05±1.6	3.08±1.5	4.12±0.9	3.51±2.1	**0.017**[*2,3,4]
PLR	165±73	143±47	135±91	155±54	0.061
NMR	11.4±4.8	11.4±4.3	10.5±5.2	10.9±4	0.488

Results are given in mean ±SD; [a]: The Kruskal-Wallis test was used for the comparison of the groups; For pairwise comparisons, the Mann-Whitney U test was used; *: P value of <0.05 was considered significant. (Pairwise comparisons of groups; [1]: BMI <25 vs BMI 25-30; [2]: BMI <25 vs BMI 30-35; [3]: BMI <25 vs BMI >35, [4]: BMI 25-30 vs BMI 30-35, [5]: BMI 25-30 vs BMI>35; BMI: body mass index; WBC: White blood cell; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; NMR: neutrophil/monocyte ratio).

DISCUSSION AND CONCLUSION

In this study, we hypothesized that routine hemogram and biochemical inflammatory parameters in patients with KOA were associated with the BMI of patients. In this study, according to the severity of the disease, we found that blood CRP and NLR levels statistically significantly increased in the severe KOA group compared to the mild KOA group; there were no significant differences in the other parameters between the two groups. Additionally, according to the BMI of patients, there was no significant difference in any of the parameters among the four groups. However, blood NLR, and NMR levels statistically significantly increased in patients with BMI>30 in the mild KOA group.

OA is a progressive condition affecting joints and surrounding tissues, marked by cartilage degradation and alterations in the subchondral bone. As its frequency rises, OA has grown to be a significant health issue. With the rise in obesity and the aging population, there have been no laboratory results linked to OA in recent years, which has become a significant issue. Because of this, researchers are now concentrating on the availability of novel biomarkers for the early diagnosis of the illness. Although OA has always been described as a noninflammatory disease, new research indicates that low-grade inflammation may be involved in the pathogenesis of the condition.[1,2,10]

KOA is a common form of OA characterized by the degradation of cartilage tissue and joint structures. It is also associated with changes in the subchondral bone.[1] KOA results in muscle stiffness. It has an impact on quality of life and physical activity. Furthermore, it is linked to a considerable financial burden concerning the costs associated with its treatment. Obesity is associated with many comorbidities, encompassing cardiovascular disease, type 2 diabetes, high blood pressure, OA and cancer. Obesity is a common metabolic disease that is a major cause of morbidity and mortality.[18] Low-grade systemic inflammation is known to result from obesity. Excess weight can lead to joint destruction due to mechanical stress on the joints. This is the cause of OA. The pathogenic features of obesity and OA are the same: As obesity develops, the risk of OA increases, and inflammation may play a role in this connection.[6] Being overweight puts an increased strain on the joints, which can lead to stress and the breakdown of the cartilage, resulting in OA. Weight loss was shown to significantly improve KOA symptoms by Christensen et al.[19] In the study by Peker et al., which involved only female patients, body composition analysis based on bioelectrical impedance analysis was conducted on patients with obesity and KOA. It was found that patients with

gonarthrosis had higher percentages of body fat and leg fat mass, while their lean mass was lower. The study concluded that in individuals with obesity and gonarthrosis, weight loss should primarily target fat tissue.[20] According to a recent study, obese people were about twice as likely to have hand OA as people of average weight.[8] These findings suggest that there may be a link between obesity and OA. The link between obesity and increased systemic inflammation has been well-documented, with studies showing that obesity is associated with elevated inflammatory markers such as CRP and NLR. Our study supports this connection by demonstrating increased NLR and NMR levels in obese patients (BMI > 30) with mild KOA. This is consistent with previous research highlighting the inflammatory role of obesity.

WBC counts and subtypes have been suggested as biological markers of inflammation in several diseases. These markers, which can be obtained without easily adding economic burden to hemogram, have gained importance in many diseases such as cardiovascular diseases, end-stage renal disease, cerebrovascular diseases, and inflammatory diseases. Meanwhile, many studies have shown NLR, PLR and NMR levels to indicate systemic inflammation.[12-16]

Recently, routine hemogram parameters, especially in the case of inflammatory diseases, have become the focus of researchers as a marker of inflammation because of the advantage that they can be easily obtained without bringing an additional economic burden. In recent years, PLR has been recognized as an important biomarker to detect inflammation in cardiovascular diseases, many cancers, cerebrovascular diseases and many inflammatory diseases such as COVID-19, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), OA, ulcerative colitis (UC), and Familial Mediterranean Fever (FMF).[21-25] In autoimmune diseases, while platelet count usually increases, lymphocyte count decreases. An increase in the PLR ratio has been found to be associated with disease activity in RA and SLE and disease severity in psoriasis.[23,24] Atar et al. found no significant relationship between OA and PLR, which aligns with our results. This could be due to differences in patient demographics and study designs.[26] Additionally, while Shi et al. found significant increases in PLR among KOA patients compared to controls, they did not find a correlation with disease severity, suggesting potential variability in inflammatory markers.[15] Similarly, Hira et al. found a significant increase in the PLR ratio in patients with OA disease.[27] In another study performed by Tasoglu et al., it was concluded that the PLR ratio is an important indicator of the severity of the disease in hip OA patients.[28] In this study, although an increase in serum PLR level was detected in severe KOA patients compared to mild KOA patients, it did not reach a statistically significant level. At the same time, when we divided the patients according to BMI, no significant increase was detected.

Similar to PLR, NMR is a routine blood test. It can be used as a marker of systemic inflammation in many inflammatory diseases.[11-13] Liu et al. showed for the first time that NMR is effective in differentiating between infected patients without lupus nephritis (LN) and healthy individuals or in differentiating between an infection from a flare in patients with LN.[13] The ability of admission NMR to accurately predict in-hospital mortality in patients with severe COVID-19 was first demonstrated by Rizo-Téllez et al.[14] Shi et al. showed that NMR can be used as a potential marker for the severity of KOA as an independent factor.[15] In this study, an increase in serum NMR level was detected in severe KOA patients compared to mild KOA patients. At the same time, when we divided the patients according to BMI, serum NMR levels statistically significantly increased in patients with BMI>30 in the mild OA groups.

NLR is another routine blood test that can serve as a marker of systemic inflammation in many inflammatory diseases.[21,22,24,25] For example, studies have shown elevated blood NLR levels in patients with active UC compared to control subjects, indicating that NLR can distinguish UC patients from healthy individuals and reflect the state of the intestinal mucosa, especially when colonoscopy is not an option.[25] Additionally, blood NLR levels were found to be higher in RA patients compared to controls and were connected to CRP, ESR, and disease activity. There was also a substantial association between the DAS 28-ESR score and PLR and NLR.[24] Dincer et al.'s study further highlighted the utility of blood NLR levels as an indicator of subclinical inflammation in patients with FMF.[21] Tasoglu et al.'s pioneering work in the literature identified blood NLR levels as a novel and promising marker for inflammation, particularly serving as an indicator of KOA severity.[29] Supporting the inflammatory hypothesis in OA pathogenesis, another study demonstrated higher blood NLR levels in the OA group compared to the control group. The observed increase in CRP and NLR levels in severe KOA patients may be attributed to chronic inflammation's impact on joint tissues. Chronic inflammation can lead to cartilage degradation and changes in the subchondral bone, which are characteristic features of KOA. In our previous study, we found that although the mean blood NLR was significantly elevated in KL grade 4 compared with the other grades, there was no statistical difference between patients with KOA and healthy controls.[30] Similarly, in our previous study, we found that blood NLR levels statistically signifi-

cantly increased in the severe KOA group compared to the mild KOA group, and we also found that blood NLR levels statistically significantly increased in patients with BMI>30 in the mild KOA group. Our findings support the emerging view that low-grade systemic inflammation is involved in the pathogenesis of OA, challenging the traditional view of OA as a purely non-inflammatory condition. This aligns with the broader theoretical framework linking obesity, inflammation, and metabolic disorders with chronic diseases like OA. Based on our findings, we propose a model where systemic inflammation acts as a mediator between obesity and KOA severity. In this model, inflammatory markers such as NLR and NMR can serve as indicators of disease progression and severity, providing a basis for early intervention and personalized treatment strategies.

The most significant limitation of our study is the relatively small sample size for KOA, which has become a significant health problem in recent years. The single-center design also limits the generalizability of our findings. Therefore, our results should be supported by prospective studies with larger patient populations and histological research.

In conclusion, despite some limitations, our study has shown that NLR and NMR ratios may be low-cost laboratory tests that can be used as markers in obesity-related KOA. The data obtained from this study suggest that NLR and NMR could provide a new perspective on the relationship between obesity and mild KOA in clinical settings. Future research should focus on larger, multicenter studies to validate these findings and explore the underlying mechanisms in more detail.

Ethics Committee Approval: Our study was approved by the Atatürk University Ethics Committee (Date: 30.11.2017, Decision no: B.30.2.ATA.0.01.00/91). The study was conducted in accordance with the Helsinki Declaration of 1975, which was revised in 2000.

Conflict of Interest: No conflict of interest was declared by the authors.

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