











# The correlation between serum YKL-40, proteinuria and inflammation in patients with systemic lupus erythematosus

## Sistemik lupus eritematozuslu hastalarda serum YKL-40, proteinüri ve inflamasyon düzeyi arasındaki ilişki

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### ABSTRACT

**Aim:** YKL-40 is a protein associated with acute and chronic inflammation and cancer. Neutrophils, macrophages, and cancer cells normally produce it. It plays a role in cell proliferation, differentiation, angiogenesis, inflammation, and extracellular matrix remodeling. It is also a marker of endothelial dysfunction and atherosclerosis. Serum YKL-40 has been reported to be associated with proteinuria in diabetic and renal transplant patients. In this study, we aimed to investigate, for the first time in the literature, the relationship between the amount of proteinuria and inflammatory markers and YKL-40 in patients with systemic lupus erythematosus (SLE).

**Material and Methods:** Fifty-one patients with SLE who presented to the adult nephrology outpatient clinic between June 2022 and January 2023 were included in the study. Blood and urine test results were obtained from the patients' routine examinations. ELISA was used to determine YKL-40.

**Results:** The mean age of the patients was 38±14 years and 94% were female. The median creatinine was 0.72 (0.36-2.62) mg/dl, the mean estimated glomerular filtration rate was 99±31 ml/min, the mean C-reactive protein (CRP) was 8±7 mg/L, the median erythrocyte sedimentation rate (ESR) was 14.5 (4-72) mm/hour, the median amount of proteinuria was 190 (69-4959) mg/g and the mean YKL-40 was 12.9±9.2 pg/ml. In correlation analysis, YKL-40 was positively correlated with glucose, CRP, and ESR [respectively (p=0.01, r=0.26), (p=0.02, r=0.06), (p=0.01, r=0.11)], and negatively correlated with calcium, albumin, in-

### ÖZ

**Amaç:** YKL-40; akut ve kronik inflamasyon yanında kanser ile ilişkili bir proteindir. Hücre proliferasyonu, diferansiasyonu, anjiyogenez, inflamasyon ve ekstrasellüler matris remodellinginde görevli bu proteinler normalde nötrofiller, makrofağlar ve kanser hücreleri tarafından üretilir. Ayrıca endotel disfonksiyonunun ve aterosklerozun da bir göstergesidir. Diyabetik ve böbrek nakilli hastalarda serum YKL-40 düzeyinin proteinüri ile ilişkili olduğu bildirilmiştir. Biz de bu çalışmada, literatürde ilk defa, Sistemik Lupus Eritematozus (SLE) hastalarında YKL-40 düzeyi ile proteinüri miktarı ve inflamasyon belirteçleri arasındaki ilişkiyi incelemeyi amaçladık.

**Gereç ve Yöntemler:** Çalışmaya Haziran 2022–Ocak 2023 tarihleri arasında Nefroloji Polikliniğe başvuran 51 SLE hastası dahil edildi. Kan ve idrar tetkik sonuçları hastaların rutin tetkiklerinden elde edildi. YKL-40 düzeyi ELISA yöntemiyle ölçüldü.

**Bulgular:** Hastaların yaş ortalaması 38±14 yıl olup %94'ü kadındı. Ortanca kreatin 0.72 (0.36-2.62) mg/dl, ortalama tahmini glomerüler filtrasyon hızı 99±31 ml/dk, ortalama C-reaktif protein (CRP) 8±7 mg/L, ortanca eritrosit sedimentasyon hızı (ESH) 14.5 (4-72) mm/sa, ortanca proteinüri miktarı 190 (69-4959) mg/g ve ortalama YKL-40 düzeyi 12.9±9.2 pg/ml'di. Korelasyon analizinde, YKL-40; glukoz, CRP, ESH ile pozitif korele [sırasıyla (p=0.01, r=0.26), (p=0.02, r=0.06), (p=0.01, r=0.11)], kalsiyum, albümin, intakt parathormon ve kompleman-3 düzeyi ile negatif korele [sırasıyla (p<0.001, r=-0.41), (p=0.01, r=-0.37),

tact parathyroid hormone, and complement-3 [respectively ( $p<0.001$ ,  $r=-0.41$ ), ( $p=0.01$ ,  $r=-0.37$ ), ( $p=0.01$ ,  $r=-0.41$ ), ( $p<0.001$ ,  $r=-0.52$ )]. No correlation was found between YKL-40 and the amount of proteinuria ( $p=0.68$ ,  $r=0.18$ ).

**Conclusion:** Serum YKL-40 was found to be associated with inflammatory markers such as CRP and ESR in SLE patients, but not with the amount of proteinuria.

**Keywords:** Inflammation, proteinuria, systemic lupus erythematosus, Ykl-40

( $p=0.01$ ,  $r=-0.41$ ), ( $p<0.001$ ,  $r=-0.52$ )] bulundu. YKL-40 düzeyi ile proteinüri miktarı arasında ilişki tespit edilmedi ( $p=0.68$ ,  $r=0.18$ ).

**Sonuç:** SLE hastalarında YKL-40 düzeyi ile CRP ve ESH gibi inflamasyon markerları arasında ilişki bulunmakla birlikte, proteinüri miktarıyla bir ilişki bulunamamıştır.

**Anahtar Kelimeler:** İnflamasyon, proteinüri, sistemik lupus eritematosus, Ykl-40

## Highlights

- YKL-40 is a protein associated with cell proliferation, differentiation, angiogenesis, and inflammation.
- YKL-40 is produced by neutrophils, macrophages, and cancer cells and is an indicator of endothelial dysfunction and atherosclerosis.
- Serum YKL-40 levels have been reported to be associated with proteinuria in diabetic and kidney transplant patients.
- Our study found a correlation between YKL-40 levels and inflammation markers in Systemic Lupus Erythematosus patients, but no correlation with the amount of proteinuria.

## INTRODUCTION

YKL-40, also known as chitinase-3-like protein-1, has a glycoprotein structure and the 40 in its name comes from its molecular weight of 40 kDa. It is known to be associated with acute and chronic inflammation and even cancer (1). Neutrophils, macrophages, and cancer cells normally produce it. It plays a role in cell proliferation and differentiation, angiogenesis, inflammation, and extracellular matrix remodeling (2). It is also a marker of endothelial dysfunction and atherosclerosis (1).

YKL-40 is associated with the amount of albuminuria in patients with type 1 and type 2 diabetes mellitus (DM), and it has been reported that high serum YKL-40 may predict all-cause mortality in these patients (3, 4). It has also been reported to be associated with proteinuria in renal transplant patients (5).

YKL-40 is known to be high in patients with nephrotic syndrome. Moreover, an association between YKL-40 and arterial stiffness has been previously reported in the literature (6). It has also been reported that YKL-40 is higher in patients with end-stage renal disease (ESRD) on dialysis and not on dialysis compared to the healthy population, and that YKL-40 increases with decreasing estimated glomerular filtration rate (eGFR) in ESRD patients (7).

In addition, in recent years, the fact that serum YKL-40 levels may increase in autoinflammatory diseases and may even be related to disease activity has become a popular research topic (8). For all these reasons, high YKL-40 may be a practical and useful follow-up parameter, as it can give an idea of prognosis and disease activation in diseases with renal involvement.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by inflammation and immune-mediated damage in multiple organ systems, including the mucocutaneous, musculoskeletal, hematological, and kidney systems. Approximately 40% of SLE patients develop lupus nephritis, and an estimated 10% of individuals with lupus nephritis develop end-stage renal disease within 10 years (9). Therefore, disease monitoring and early detection of renal involvement are crucial for patient surveillance. In this study, we aimed to investigate, for the first time in the literature, the relationship between YKL-40 and the amount of proteinuria and inflammatory markers in SLE patients.

## MATERIAL and METHODS

This cross-sectional study was conducted at Kahramanmaraş Sutcu Imam University Faculty of Medicine Nephrology Outpatient Clinic. The study was approved by the Ethics Committee of Kahramanmaraş Sutcu Imam University Faculty of Medicine on 14.02.2022 with the number 2022/17. Patients were informed before the study and informed consent forms were signed. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Patients over 18 years of age who presented to the Adult Nephrology Outpatient Clinic between June 2022 and January 2023 and were diagnosed with SLE were included in the study. The 2012 SLICC criteria were used to diagnose SLE (10). Patients with additional diseases known to affect serum YKL-40, including DM, renal transplantation, coronary artery disease, malignancy, additional inflammatory disease, and local or systemic infection were not included in the study.

Patients' age, gender, and additional disease information were obtained from the hospital's automated system files; blood and urine test results were obtained from patients' test results during routine examinations. Serum YKL-40 was assessed by ELISA (Fine Test, Wuhan, China). The kit was able to detect serum YKL-40 in the range of 62.5-4000 pg/ml.

**Statistical Analysis:** SPSS 20.0 was used to analyze the study data. Continuous variables determined by measuring patients were expressed as mean±SD and categorical data determined by counting were expressed as numbers of patients or percentages. Kolmogorov-Smirnov and/or Shapiro-Wilk tests were used to analyze the normal distribution of continuous data. Pearson or Spearman correlation analysis was used for correlation analysis, depending on the distribution characteristics of the data. A p-value of less than 0.05 was considered statistically significant.

**RESULTS**

Fifty-one patients with SLE were included in the study. The mean age of the patients was 38±14 years and 94% were

**Table 1:** General characteristics and laboratory measurements of the patients

Parameters	Mean±SD, Median or n(%) (n=51)
Age (y)	38±14
Gender (Female) (%)	94.1
Glucose (mg/dL)	86.5 (72-252)
BUN (mg/dL)	12 (5-98)
Creatinine (mg/dL)	0.72 (0.36-2.62)
eGFR (ml/dk)	99±31
Sodium (mmol/L)	140 (130-145)
Potassium (mmol/L)	4.3±0.4
Calcium (mg/dL)	9.05 (7.40-9.80)
Albumin (mg/dL)	41.5 (18-47)
Ferritin (mg/L)	44 (6-598)
iPTH (pg/mL)	45 (8-154)
Proteinuria (mg/g)	190 (69-4959)
C3 (mg/L)	0.79±0.22
C4 (mg/L)	0.15±0.06
ANA (%)	86.3
Anti-dsDNA (%)	7.8
CRP (mg/L)	8±7
ESR (mm/hour)	14.5 (4-72)
YKL-40 (pg/mL)	12.9±9.2

Data are presented as mean±SD , median (min–max), or n (%), as appropriate.

**BUN:** blood urea nitrogen, **eGFR:** estimated glomerular filtration rate, **iPTH:** intact parathyroid hormone, **C3:** complement 3, **C4:** complement 4, **CRP:** C-reactive protein, **ESR:** erythrocyte sedimentation rate

female. The median creatinine was 0.72 (0.36-2.62) mg/dl, the mean eGFR was 99±31 ml/min, the mean C-reactive protein (CRP) was 8±7 mg/L, the median erythrocyte sedimentation rate (ESR) was 14.5 (4-72) mm/hour, the median amount of proteinuria was 190 (69-4959) mg/g and the mean YKL-40 was 12.9±9.2 pg/ml. The general characteristics and laboratory results of the patients are detailed in Table 1.

A review of patient files revealed that 21 patients underwent kidney biopsies due to suspected lupus nephritis. The presence of lupus nephritis was confirmed by kidney biopsy in 20 patients. Only one patient's biopsy was not definitively evaluated due to insufficient sample size. In three patients with clinical suspicion of lupus nephritis, kidney biopsies were not performed due to reasons such as contraindications to kidney biopsy, patient refusal to undergo the procedure, or low platelet count at presentation.

In the correlation analysis, YKL-40 was positively correlated with glucose (p=0.01, r=0.26), CRP (p=0.02, r=0.06), and ESR (p=0.01, r=0.11); and negatively correlated with calcium (p<0.001, r=-0.41), albumin (p=0.01, r=-0.37), intact parathyroid hormone (iPTH) (p=0.01, r=-0.41) and complement 3 (C3) (p<0.001, r=-0.52). No correlation was found between YKL-40 and the amount of proteinuria (p=0.68, r=0.18). Detailed information on the correlation analysis is shown in Table 2.

**Table 2:** Correlation analysis for YKL-40

Parameters	p	R
Age (y)	0.83 <sup>a</sup>	-0.05
Glucose (mg/dL)	0.01 <sup>b</sup>	0.26
BUN (mg/dL)	0.30 <sup>b</sup>	0.08
Creatinine (mg/dL)	0.46 <sup>b</sup>	-0.06
Sodium (mmol/L)	0.09 <sup>b</sup>	-0.13
Potassium (mmol/L)	0.73 <sup>a</sup>	0.04
Calcium (mg/dL)	<0.001 <sup>b</sup>	-0.41
Albumin (mg/dL)	0.01 <sup>b</sup>	-0.37
Ferritin (mg/L)	0.06 <sup>b</sup>	0.03
iPTH (pg/mL)	0.01 <sup>b</sup>	-0.41
Proteinuria (mg/g)	0.68 <sup>b</sup>	0.18
C3 (mg/L)	<0.001 <sup>a</sup>	-0.52
C4 (mg/L)	0.21 <sup>a</sup>	-0.15
CRP (mg/L)	0.02 <sup>a</sup>	0.06
ESR (mm/hour)	0.01 <sup>b</sup>	0.11

<sup>a</sup>:Pearson <sup>b</sup>:Spearman correlation analysis

**BUN:** blood urea nitrogen, **iPTH:** intact parathyroid hormone, **C3:** complement 3, **C4:** complement 4, **CRP:** C-reactive protein, **ESR:** erythrocyte sedimentation rate

## DISCUSSION

Our study is the first to investigate the relationship between serum YKL-40 and the extent of proteinuria and inflammatory markers in SLE patients. Previous studies in the literature have shown that YKL-40 has a high diagnostic potential, especially in young female patients, and can provide insight into disease activation. However, these studies did not evaluate the amount of proteinuria. In this respect, our study is the first in the literature. As a result of our study, we found that YKL-40 was associated with inflammatory markers such as CRP and ESR in SLE patients, but not with the amount of proteinuria.

It has been noted that the increase in circulating YKL-40 is more pronounced in patients with coronary artery disease and that this increase in patients with coronary artery disease may be associated with major cardiovascular events (11, 12). El-Ghorab et al. reported that serum YKL-40 level is a highly sensitive predictor of atherosclerosis in CKD patients, with a sensitivity of 74% in CKD (13).

An attempt has been made to explain the relationship between proteinuria and CVD risk by the fact that systemic endothelial dysfunction also causes vascular damage in the kidneys and increases proteinuria (14). Similarly, Tatar et al. reported that there is a correlation between YKL-40 and proteinuria in kidney transplant recipients and that this correlation may play a role in the pathogenesis of cardiovascular damage in this patient group (5). However, the relationship between YKL-40 and proteinuria is unclear. Proteinuria alone does not always indicate renal damage but is associated with increased systemic vascular permeability (15). The increase in vascular permeability in proteinuric patients may be due to endothelial dysfunction. The relationship between endothelial dysfunction markers and micro and macroalbuminuria has been attempted to be explained in this way (16). The main idea of our study was that YKL-40 is an indicator of endothelial dysfunction and atherosclerosis and therefore can give an idea about proteinuria.

This relationship has been studied in different patient groups before in the literature. In a study conducted by Kocyigit et al. on patients with nephrotic syndrome, it was found that there is a relationship between serum YKL-40 and endothelial dysfunction and arterial stiffness and that the amount of proteinuria is significantly higher in patients with nephrotic syndrome with high serum YKL-40, therefore serum YKL-40 may be an indicator of proteinuria in patients with nephrotic syndrome (6). A study by Persson et al. found that high serum YKL-40 in patients with type 2 DM and increased proteinuria could predict all-cause mortality (4). Similarly, other studies in the literature have reported an association between the degree of albuminuria and serum and/or urinary YKL-40 in diabetic patients

(17-19). In our study, unlike previous studies, we found no similar association between YKL-40 and proteinuria in SLE patients. The fact that proteinuria was assessed using spot urine and the small sample size may be a contributing factor. Because our study was conducted retrospectively, upon reviewing patient files, we observed that 24-hour urine data were missing. This was due to the difficulty of collecting 24-hour urine samples and the fact that routine outpatient clinic follow-ups were performed using the first morning urine sample, which is known to provide the closest proteinuria results, rather than the 24-hour urine sample. Although similar results are known to be obtained, we may not have been able to detect a possible association because the 24-hour urine sample was not used. We also believe that the small sample size may be another factor, and we note this as a limitation of our study.

A study by Keskin et al. found that YKL-40 is an inflammatory marker that increases with the stage of ESRD, is associated with markers of endothelial dysfunction, and is also correlated with CRP and uric acid (7). A study by Lorenz et al. found that high YKL-40 in ESRD patients may be a marker for risk prediction of cardiovascular mortality (20). Similarly, El-Ghorab et al. reported that YKL-40 was a highly sensitive indicator of CRP, ESR, and increased carotid intima-media thickness in CKD patients, but they could not detect any relationship with ferritin and albumin levels (13). In our study, a correlation was found between YKL-40 and CRP, ESR and hypoalbuminemia, but no correlation was found with ferritin level.

There are few studies in the literature on the relationship between YKL-40 and SLE patients. A study by Ali et al. found that YKL-40 has a high diagnostic potential in SLE, especially in young women. This study reported that YKL-40 levels were associated with disease duration, anemia, thrombocytopenia, positive anti-double stranded DNA (anti-dsDNA), and antiphospholipid antibody (APL) levels. The study was conducted in juvenile SLE patients, and YKL-40 levels were reported to increase with increasing age. The relationship between SLE diagnostic criteria and YKL-40 levels was analyzed, and no association was reported with nephrological involvement (21). The study was conducted in a younger patient population and examined general renal findings such as nephrological involvement. Specific findings such as proteinuria were not examined. Furthermore, the relationship with SLE clinical findings was analyzed, but no analysis was conducted regarding markers such as ESR or CRP. In these respects, it differs from our study. A study by Gamal El-Agamy et al. reported that serum YKL-40 was higher in SLE patients than in healthy controls and that YKL-40 correlated with disease activity, CRP, ESR, and serum creatinine (22). Similarly, in our study, we observed a correlation between YKL-40 and CRP, ESR, and hypoalbuminemia which are traditional indicators of SLE activation.

The relationship between YKL-40 and various autoimmune diseases has been investigated in the literature. It has been previously reported in the literature that it can provide insight into the diagnosis, prognosis and disease activity of diseases such as Rheumatoid Arthritis, Psoriasis, Behçet's disease and Inflammatory bowel disease, in addition to SLE (8). A study by Chen et al. found that serum YKL-40 was a cytokine associated with disease activity, as were TNF- $\alpha$  and IL-6, in patients with primary Sjögren's syndrome. It was emphasized that these three cytokines are also related to CRP and ESR. In addition, serum YKL-40 is associated with lung and kidney involvement, neutrophil count, leukopenia, and anemia in these patients (23).

The first limitation of our study is the number of patients. It would be appropriate to support the issue with studies conducted in larger groups of patients. Second, proteinuria was assessed with spot urine. Another limitation is that serum YKL-40 was measured with a single assay. It is more likely that more reliable results will be obtained if serial measurements are used.

### Conclusion

Our study is the first to investigate the relationship between serum YKL-40, proteinuria, and inflammatory markers in SLE patients. We found that serum YKL-40 was associated with inflammatory markers such as CRP and ESR in SLE patients, but not with the amount of proteinuria. The small number of patients may be a factor influencing this and further studies are needed.

### Author Contributions

Study conception and design: **Ilyas Ozturk, Ozkan Gungor**; data collection: **Fatma Betul Guzel, Serhat Kura, Enes Suleyman Gun, Burak Okyar, Muhammed Seyithanoglu**; analysis and interpretation of results: **Ilyas Ozturk, Sinan Kazan, Gozde Yildirim Cetin, Orcun Altunoren, Ozkan Gungor**; draft manuscript preparation: **Ilyas Ozturk, Ozkan Gungor**. The author(s) reviewed the results and approved the final version of the article.

### Conflicts of Interest

The authors have no conflict of interest to declare.

### Ethical Approval

The study was approved by the Ethics Committee of Kahramanmaraş Sutcu Imam University Faculty of Medicine on 14.02.2022 with the number 2022/17. Patients were informed before the study and informed consent forms were signed.

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