# The Association of FGF-23, IL-1 and KIM-1 with Progression and Mortality Rates of Chronic Kidney Disease

## *Kronik Böbrek Yetmezliğinde FGF-23, IL-1 ve KIM-1 Düzeyinin Progresyon ve Mortalite Oranları ile İlişkisi*

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## ABSTRACT

**OBJECTIVE:** We aimed to evaluate the relation of serum Fibroblast Growth Factor 23 (FGF-23), Interleukin 1 beta (IL-1 beta) and Kidney Injury Molecule 1 (KIM-1) levels with progression and mortality rates of patients with CKD at the predialysis stage.

**MATERIAL and METHODS:** A total of 147 patients with CKD who presented to the Internal Medicine Department of Bagcilar Training and Research Hospital between January and May 2012 were enrolled into the study. Hemogram analysis, biochemical parameters and serum FGF-23, IL-1 beta and KIM-1 levels were examined at initial evaluation and at the 48th month of follow-up.

**RESULTS:** Diabetes mellitus (DM) and hypertension (HT) were major causes of CKD. During the 48-month follow-up period, 51 patients (34.6%) died. A statistically significant relationship was observed between mortality rates and stage of disease, age, high levels of serum C-reactive protein (CRP) and ferritin and decreased serum albumin levels; however, the effects of gender and the presence of DM on mortality were statistically nonsignificant. Relationship of serum FGF-23, IL-1 beta and KIM-1 with magnesium as well as serum FGF-23 and IL-1 beta with uric acid and IL-1 beta with CRP were statistically significant.

**CONCLUSION:** Both initial serum levels and variations of FGF-23, IL-1 beta and KIM-1 had a nonsignificant impact on mortality of CKD patients during the 48-month follow-up period. Further studies with a higher number of participants and longer duration of follow-up are required to determine predictors of prognosis and mortality in patients with CKD.

**KEY WORDS:** Chronic kidney disease, FGF-23, IL-1 beta, KIM-1

## ÖZ

**AMAÇ:** Prediyaliz dönem kronik böbrek yetmezlikli (KBY) hastalarda progresyon ve mortalite oranları ile serum Fibroblast Growth Factor 23 (FGF-23), Interleukin 1 beta (IL-1 beta) ve Kidney Injury Molecule 1 (KIM-1) arasındaki ilişki incelendi.

**GEREÇ ve YÖNTEMLER:** Ocak ve Mayıs 2012 yılları arasında Bağcılar Eğitim ve Araştırma Hastanesine başvuran 147 KBY tanılı hasta çalışmaya dahil edildi. Çalışmanın başlangıcı ve 48. ayında hastaların serum FGF-23, IL-1 beta ve KIM-1 düzeyleri ile hemogram ve biyokimyasal parametreleri incelendi.

**BULGULAR:** Diabetes mellitus (DM) ve hipertansiyon (HT), KBY'nin en sık 2 nedeni idi. 48 aylık takip süresi boyunca 51 hasta (%34.6) kaybedildi. Mortalite oranları ile hastalık evresi, yaş, yüksek C-reaktif protein (CRP) ve ferritin ve düşük albumin düzeyleri arasında anlamlı ilişki saptandı fakat cinsiyet ve DM varlığının mortalite üzerine etkisi anlamlı izlenmedi. Serum FGF-23, IL-1 beta ve KIM-1 ile magnezyum, FGF-23 ve IL-1 beta ile ürik asit ve IL-1 beta ile CRP arasındaki ilişkiler anlamlı idi.

**SONUÇ:** KBY'li hastalarda mortalite oranları ile serum FGF-23, IL-1 beta ve KIM-1'in hem başlangıç hemde 48. ay incelemeleri arasındaki ilişki izlenmezken daha geniş çaplı ve daha uzun takip süreli çalışmalarla KBY progresyon ve mortalite prediktörlerinin belirlenmesine ihtiyaç bulunmaktadır.

**ANAHTAR SÖZCÜKLER:** Kronik böbrek yetmezliği, FGF-23, IL-1 beta, KIM-1

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## INTRODUCTION

Chronic kidney disease (CKD) is defined as irreversible functional renal insufficiency lasting for at least 3 months and affects more than 2 million people worldwide (1-3). According to current data, 10% of all individuals have a renal disorder at various stages (4,5).

Due to inadequate awareness to CKD, patients are usually diagnosed at the end stage renal disease (ESRD) phase, leading to an increased morbidity-mortality rate, lower quality of life, and high cost. A number of factors including age, gender, race, comorbidity, inflammatory conditions, and the C-reactive protein (CRP), ferritin, albumin, and calcium (Ca) levels are involved in the pathophysiology of CKD and have an important impact on progression rates (6,7). Besides CRP and ferritin that indicate severity of inflammation, the relationship of FGF-23, IL-1 beta and KIM-1 with acute and chronic renal injury has been established by experimental animal studies (8,9). Widespread use of these markers in the diagnosis and follow-up of patients with CKD may be related to early diagnosis and decreased cost and mortality rate.

A practical marker that can help evaluate disease severity and predict the progression of CKD is lacking. In the present study, we aimed to examine the relationship of serum FGF-23, IL-1 beta and KIM-1 levels with progression and mortality rates in CKD patients at the predialysis stage.

## MATERIAL and METHODS

A total 147 patients consisting of 84 males (57.1%) and 63 females (42.9%), aged between 41 and 96 years, who presented to the Bagcilar Education and Research Hospital between January 2012 and May 2012 were enrolled. Patients on renal replacement therapy (RRT), pregnancy or co-existing malignancy were excluded. Demographic data including age, weight, height and occupation were recorded by interviewing the patients or first-degree relatives, and evaluating medical records. The ethics committee of Bagcilar Education and Research Hospital approved the study. Written informed consent was obtained from all participants. The study was performed in accordance with Declaration of Helsinki. The clinical studies registration number was 2015/404.

Blood samples were collected after a 12-hour fasting period and stored at -80°C after centrifugation at 3000 rpm for 15 minutes to evaluate FGF-23, IL-1 beta and KIM-1 levels. Biochemical variables including serum glucose, urea, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), Ca, sodium (Na), potassium (K), magnesium (Mg), total protein, albumin, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglyceride were analyzed by the photometric method with the Siemens Advia 1800 device (Siemens Healthcare Diagnostics, Kobe, Japan). Parameters including HbA1c, insulin, ferritin, parathormone (PTH) and thyroid stimulating hormone (TSH) were analyzed by the chemiluminescence immunoassay method in a Siemens Advia Centaur device (XE-5000, Sysmex Corp. Kobe, Japan). Urine analysis was performed by the spectrophotometric method in a Siemens Advia 1800 device (XE- 5000, Sysmex Corp. Kobe, Japan). Hemogram was performed in blood samples that were taken into tubes with EDTA using an automatic blood counter (XE-5000; Sysmex Corp, Kobe, Japan). Biochemical and hormonal parameters were examined simultaneously with the study.

Serum levels of FGF-23, IL-1 beta and KIM-1 were analyzed by the Elisa method using commercially available kits according to instructions of manufacturer. Serum specimens and standards with biotin were put into a microtest cartridge coated with antihuman kit antibody. Subsequently, streptavidin-horseradish peroksidase (HRP) enzyme conjugate was added to the cartridge to remove non-aligned antihuman kit antibody. After incubation, the intensity of the color was spectrophotometrically analyzed at 450 nm wave length.

Urine analysis was performed by the spectrophotometric method in the Siemens Advia 1800 device (XE-5000, Sysmex Corp. Kobe, Japan). Urinary albumin was measured by the immunoturbidimetric method in the Cobas auto analyzer (Roche Diagnostics, Germany). Urinary creatinine was analyzed using the Aeroset autoanalyser (Abbott Laboratories Inc., Abbott Park, IL, USA).

The height and weight of participants were measured with the Tanita Body Composition Analyzer (Tanita Corporation of America, Illinois, USA). The body mass index (BMI) was calculated as weight/height$^2$ (kg/m$^2$). A body mass index (BMI) $\geq$ 30 kg/m$^2$ was defined as obesity.

### Statistical Analysis

Data were analyzed using the SPSS for Windows computer program (release 22.0; SPSS Inc., Chicago, IL, USA ). All data were expressed as the mean ± SD. Differences between the study groups were analyzed by using Student's t-test. Quantitative data were analyzed by the chi-square test. Pearson correlation analysis and Spearman's rho correlation analysis were used to evaluate the correlation of variables. The variables significant in univariate analysis were included in multivariate logistic regression analysis (only significant correlation coefficients are reported). Survival rates were evaluated by Kaplan-Meier analysis, ROC and the Log Rank test. A p value $< 0.05$ was considered to be statistically significant.

## RESULTS

The percentage of male and female participants were 57.1% (n=84) and 42.9% (n=63); respectively. The mean age was 65.38±10.47, ranging from 41 to 96 years. At the end of the 48-month follow-up, 51 patients (34.7%) died. Considering the

etiologic factor, the distribution of diabetes mellitus (DM) and hypertension (HT) were 49.6% and 31.9%, respectively.

The distribution of the stages of patients were as follows; stage I 15.0% (n=22), stage II 43.5% (n=64), stage III 22.4% (n=33), stage IV 10.9% (n=16), and stage V 8.2% (n=12).

A negative correlation was found between FGF-23 and uric acid, and a positive correlation was present between FGF-23 and Mg (p:0.036 and p:0.029, respectively). IL-1 beta was negatively correlated with uric acid and Na, and positively correlated with Mg and CRP (p:0.009, p:0.007 and p:0.034, p:0.024, respectively). A significant and positive relation was determined between KIM-1 and Mg (p: 0.021) (Table I).

During the study period, 51 of 147 patients (34.7%) consisting 30 males and 21 females died. The survival rates were similar in the genders (p:0.829).

**Table I:** Correlation of FGF-23, IL-1 beta and KIM-1 levels with biochemical parameters at initial evaluation.

| | | FGF-23 | IL-1 beta | KIM-1 |
|---|---|---|---|---|
| **Uric acid (mg/dL)** | r | -0.176 | -0.216 | -0.139 |
| | p | 0.036* | 0.009** | 0.099 |
| **$Mg^{+2}$ (mg/dL)** | r | 0.329 | 0.321 | 0.346 |
| | p | 0.029* | 0.034* | 0.021* |
| **$Na^{+}$ (mmol/L)** | r | -0.074 | -0.228 | -0.154 |
| | p | 0.386 | 0.007** | 0.070 |
| **CRP (mg/L)** | r | -0.027 | 0.191 | 0.028 |
| | p | 0.748 | 0.024* | 0.742 |

**Mg:** Magnesium, **Na:** Sodium, **CRP:** C-reactive protein
Spearman's rho test * p<0.05 **p<0.01

Survivors had significantly higher baseline levels of glomerular filtration rate (GFR), Ca, albumin and hemoglobin. In the baseline evaluation, age, urea, creatinine, uric acid, ferritin, CRP and urine protein creatinine rate (PCR) levels of nonsurvivors were significantly higher. Survivors and nonsurvivors had similar baseline FGF-23, IL-1 beta, KIM-1, phosphorus (P), Mg, leukocyte (WBC) and thrombocyte (PLT) values (Table II, Figure 1).

The number of CKD patients with major comorbidities like DM and HT were significantly higher in patients at stage 2 and 3 compared to stage 4 or 5, which is the probable explanation of the higher mortality rates in stage 2 and 3 (Table III). In Table IV, data regarding the causes of mortality in all patients are given.

We failed to determine a significant correlation between initial stage and mortality rate. Similarly, no significant association was observed between baseline FGF-23, IL-1 beta and KIM-1 and the stage of CKD.

The change in GFR from the baseline evaluation to the endpoint was nonsignificantly related to the variation of FGF-23, IL-1 beta and KIM-1 levels. Table V shows the frequency of mortality according to stage.

## DISCUSSION

The etiology of CKD varies according to age, race and gender (10,11). According to the register of the Turkish Society of Nephrology in 2014, DM is the leading cause of ESRD patients on hemodialysis (HD) (33.5%) followed by HT (27.1%), glomerulonephritis (6.1%), polycystic kidney disease (4.8%), amyloidosis (2.4%), and unknown causes (14.9%) (12). On the other hand, HT is the most common cause (31.3%) in peritoneal dialysis (PD) patients followed by DM (22.0%), glomerulonephritis (8.7%), polycystic kidney disease (5.3%), tubulointerstitial nephritis (2.1%), amyloidosis (2.0%), and unknown causes (13.6%) (12).

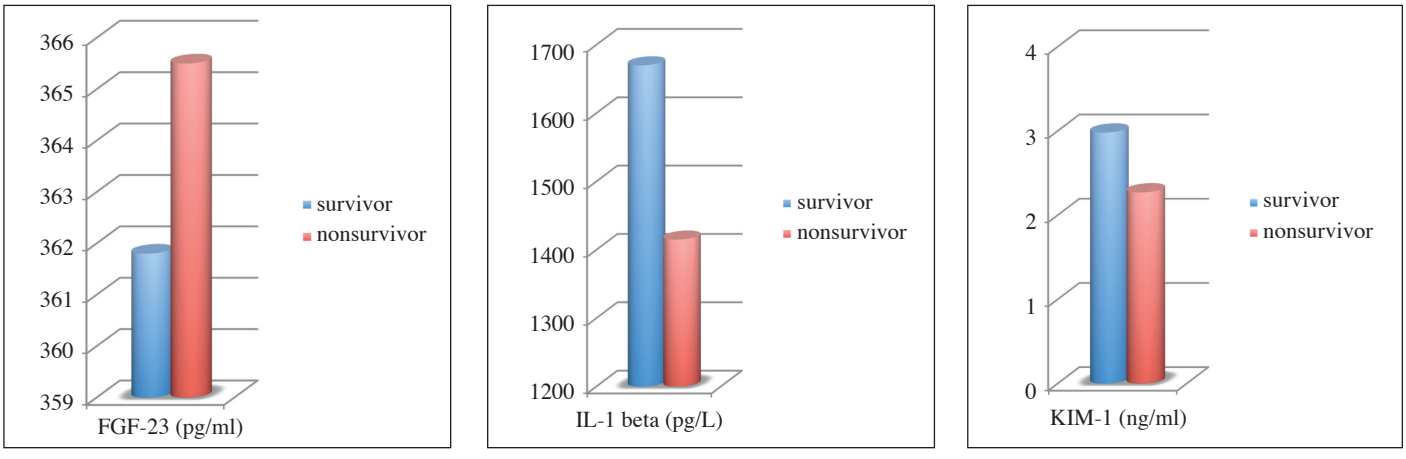


***Figure 1:*** *Mean FGF-23, IL-1 beta and KIM-1 levels at initial evaluation of survivors and nonsurvivors (p=0.170, p=0.221 and p=0.829; respectively)*

**Table II:** Comparison of demographic and laboratory parameters of survivors and nonsurvivors.

| | Mortality | | p |
|---|---|---|---|
| | **Survivor** | **Nonsurvivor** | |
| | **Mean±SD** | **Mean±SD** | |
| Age (year) | 63.57±9.94 | 68.78±10.7 | [1]**0.004**** |
| GFR (ml/min) | 70.24±28.13 | 50.33±37.23 | [1]**0.001**** |
| Urea(mg/dL) | 55.36±40.9 | 91.9±62.88 | [2]**0.001**** |
| Creatinine (mg/dL) | 1.41±1.28 | 2.47±2.51 | [2]**0.001**** |
| Uric acid (mg/dL) | 6.27±1.86 | 7.43±3.38 | [1]**0.028*** |
| $Ca^{+2}$ (mg/dL) | 9.24±0.68 | 8.79±0.7 | [1]**0.001**** |
| P (mg/dL) | 3.71±0.89 | 4.11±1.79 | [1]**0.133** |
| $Mg^{+2}$ (mg/dL) | 2.13±0.38 | 2.12±0.35 | [1]**0.921** |
| Albumin (g/dL) | 4.19±0.55 | 3.64±0.67 | [1]**0.001**** |
| Ferritin (ng/mL) | 148.71±203.98 | 267.26±327.91 | [2]**0.014*** |
| CRP (mg/L) | 25.39±36.18 | 49.43±45.2 | [2]**0.001**** |
| Urine protein/creatinine (PCR) | 606.03±1085.15 | 1364.15±2463.35 | [2]**0.002**** |
| WBC ($x10^3$ $mm^3$) | 8.52±2.53 | 9.13±3.17 | [1]**0.214** |
| HGB (g/dL) | 12.24±2.15 | 10.85±2.41 | [1]**0.001**** |
| PLT ($x10^3$ $mm^3$) | 259.22±96.59 | 229.04±102.18 | [1]**0.082** |

[1] Student t Test, [2] Mann-Whitney U Test, * p<0.05, ** p<0.01, * **GFR:** Glomerular filtration rate, **Ca:** Calcium, **P:** Phosphorus, **Mg:** Magnesium, **CRP:** C-reactive protein, **PCR:** Protein creatinine rate, **WBC:** Leukocyte, **HGB:** Hemoglobin, **PLT:** Thrombocyte.

**Table III:** Presence of major comorbidities (diabetes mellitus and hypertension) according to stage.

| | | HT+DM | | P |
|---|---|---|---|---|
| | | Yes | No | |
| Stage | Stage 1 | 19 | 3 | **0,028**** |
| | Stage 2 | 47 | 17 | |
| | Stage 3 | 18 | 15 | |
| | Stage 4 | 8 | 8 | |
| | Stage 5 | 6 | 6 | |
| Total | | 98 | 49 | |

**Pearson Chi-Square * p<0.05

**Table IV:** Causes of mortality in all patients.

| | **Frequency** | **Percent** |
|---|---|---|
| Coroner artery disease (CAD) | 15 | 29.4 |
| Chronic Kidney Disease (CKD) | 1 | 2.0 |
| Poor Health Status (PHS) | 4 | 7.8 |
| Hemorrhage | 3 | 5.9 |
| Infection | 1 | 2.0 |
| Malignancy | 3 | 5.9 |
| Total | 27 | 52.9 |
| Unknown | 24 | 47.1 |
| Total | 51 | 100.0 |

The mortality rate of patients on dialysis therapy is approximately 10-30 fold higher than the general population, probably related to advanced age and comorbidities like DM, HT, hyperlipidemia, cardiovascular diseases (CVD), and infectious and inflammatory disorders (13,14). Inflammation and increased intraglomerular pressure is the main cause of glomerular injury in CKD. Inflammatory cell infiltration in the kidney and increased proinflammatory and immunomodulatory cytokine levels play key role in progression to ESRD (6,7). Wagner et al. showed that the hepcidin level is significantly related to

**Table V:** Distribution of survivors and nonsurvivors according to stage at the initial evaluation.

| | | Mortality | | P |
|---|---|---|---|---|
| | | Survivor (n=96) | Nonsurvivor (n=51) | |
| Stage | 1 | 17 (17.7%) | 5 (9.8%) | [2]0.001** |
| | 2 | 52 (54.2%) | 12 (23.5%) | |
| | 3 | 16 (16.7%) | 17 (33.3%) | |
| | 4 | 8 (8.3%) | 8 (15.7%) | |
| | 5 | 3 (3.1%) | 9 (17.6%) | |

[1] Continuity (Yates) correction, [2] chi-square test, **p<0.01

mortality and progression of CKD but failed to demonstrate a relationship between the ferritin level and the progression and mortality rate. Similarly, advanced age, high CRP, low albumin and proteinuria have a significant impact on the progression of renal injury (8). Tsai et al. indicated a significant relationship between the CRP and ferritin level and the progression of CKD (15). In accordance with the literature, we showed a relation between mortality rates and advanced age, high CRP and ferritin levels, and low albumin values.

The association between proteinuria and decreased GFR is well known as a risk factor of CVD (13,16,17). Proteinuria causes intrinsic toxicity by leading to T lymphocyte infiltration in the glomerular capillary barrier. Thajudeen et al. and Wagner et al. determined an increased tendency to disease progression and mortality in CKD patients with proteinuria (8,18). Evaluating GFR together with proteinuria is better predictor of survival compared to analyzing GFR by itself in patients with renal cell carcinoma (19). We determined increased urine PCR in the nonsurvivor group.

Hsieh et al. and Chang et al. pointed out an association between hyperuricemia and renal disease progression and the hospitalization rate (20,21). Asicioglu et al. showed a relationship between FGF-23 and cardiovascular mortality in both a healthy population and patients with CKD, and between the uric acid level and FGF-23 in patients on RRT (22). In our study, the mortality rate was significantly associated with the uric acid level, and a correlation between FGF-23 and uric acid level has been shown. A possible explanation of the result is the poor metabolic status of patients with hyperuricemia.

Serum FGF-23 level is increased in the early stages of CKD and ESRD as shown by both human and animal studies (23,24). Liao et al. reported a relationship between FGF-23 with renal injury and bone mass in experimentally induced CKD (25). In the MMKD study, it was clearly established that FGF-23 is more significantly related to mortality than the serum P level (26). However, no significant association was determined between FGF-23 and renal disease progression and mortality, most probably due to the relatively short duration of follow-up in our study. In accordance with our study, Nitta et al. emphasized that the relation of FGF-23 with disease progression was nonsignificant in CKD patients with normophosphatemia (27).

Chronic inflammation usually accompanies ESRD due to several reasons (28). The serum level of IL-1, a proinflammatory cytokine, is elevated in patients on HD. The balance between IL-1 and antagonist of the molecule determines inflammatory response in ESRD (29). A number of studies have established that mortality and morbidity rates in ESRD are significantly correlated with the CRP and IL-1 beta levels (9). Hung et al. administered IL-ra (IL receptor antagonist) to ESRD patients, and showed that CRP and IL-6 levels were significantly decreased (28). We noted a correlation between the CRP and IL-1 beta levels.

Prajczer et al. showed an increased IL-1 beta level along with Uromodulin (Tamm-Horsfall protein) in CKD, suggesting a relationship between inflammation and proteinuria and CKD progression (30). IL-1 receptor blockage will possibly be an alternative in reducing cardiovascular morbidity and mortality rates in ESRD in the near future as proven by recent studies that indicates preventive role of IL-1 receptor blockage on cardiac remodelling (29,31). Rogacev et al. established an association between IL-1 beta and CKD progression (32). David et al. stated that IL-1 beta decreases the serum iron level and increases FGF-23 level (33). We did not observe a relationship between the mortality rate and the IL-1 beta level. Koriakova et al. determined an association between renal functional deterioration and TNF-α but not IL-1 beta in chronic glomerulonephritis (34).

Several recent prospective trials have reported increased KIM-1 levels in nephropathy of different etiologies. Kadioglu et al. claimed that KIM-1 has a predictive role in hypertensive nephropathy and is significantly related to renal injury (35). Xue et al. established a correlation between the KIM-1 level and risk of renal injury in obstructive nephropathy (36). Nowak et al. showed that basal level of KIM-1 to be a significant predictor of renal disease progression in CKD (37). In the present study, we showed that mean KIM-1 level of patients that had disease progression is nonsignificantly lower than that of patients with renal injury progression.

Carlsson et al. determined that the urinary KIM-1 level was a risk factor of cardiovascular mortality independent of GFR and albuminuria (38). Jungbauer et al. concluded that KIM-1 is a marker of cardiorenal disease and strong predictor of CKD progression (39). KIM-1 and mortality rate were nonsignificantly related in our study. Similar to our study, Castillo-Rodriguez et al. concluded that KIM-1 has no role on progression rates of CKD in the nondiabetic population (40).

Hypomagnesemia predicts decrease of GFR and increase of mortality (41). Some recent studies have determined a strong relationship between hypomagnesemia and the general and cardiovascular mortality rates in patients with CKD and those on HD (42). Silva et al. reported that hypomagnesemia and high FGF-23 were the two factors that predicted the cardiovascular mortality risk (43). The serum Mg level was correlated to the FGF-23, IL-1 beta and KIM-1 level but the association of the Mg level and mortality rate was nonsignificant. In our study, the relationship of hypomagnesemia with FGF-23, KIM-1 and IL-1 beta was shown to be related to both renal disease progression and increased cardiovascular mortality rates.

Although we did not establish a relation between disease progression and mortality rates with FGF-23, IL-1 beta and KIM-1, the lower level of KIM-1 in nonprogressive disease and the correlation of IL-1 beta and CRP suggest an indirect association of these 3 markers with disease progression and mortality rate. Our study has some drawbacks. First, the study population was small, which has important impact on the significance of the results. Second, our follow-up duration was relatively short and that may affect disease progression as well as mortality rates. Third, the rate of patients at the advanced stage in our study group was higher than in previous studies and could affect progression rates.

In conclusion, FGF-23, IL-1 beta and KIM-1 were nonsignificantly associated with progression and mortality rates in CKD. Further studies with a large number of participants and longer duration of follow-up are warranted to reach a more precise conclusion.

**Conflict of Interest Statement**

The authors declare that there is no conflict of interest with regard to this manuscript.

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