Dicle Tıp Dergisi / Dicle Med J (2026) 53 (1) : 47-57

www.diclemedj.org

Original Article / Özgün Araştırma

Association Between Neuropathic Pain and Serum Interleukin-6 and C-Reactive Protein Levels in Patients with Stage 3 to 5 Chronic Kidney Disease

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Received: 24.10.2025; Revised: 05.01.2026; Accepted: 08.01.2026

Abstract

Background: Chronic kidney disease (CKD) is commonly associated with peripheral neuropathy, yet its pathophysiology remains incompletely understood. Inflammatory markers, particularly interleukin-6 (IL-6) and C-reactive protein (CRP), are thought to play a role in the development and persistence of neuropathic pain. This study aimed to evaluate the relationship between neuropathic pain and serum IL-6 and CRP levels in patients with stage 3–5 CKD.

Methods: This prospective single-center study included 80 patients: 40 with stage 3–4 CKD and 40 with stage 5 CKD on dialysis (5D). Neuropathic pain was assessed using the PainDETECT questionnaire. Serum IL-6 and CRP levels were measured, and their associations with neuropathic pain were analyzed using correlation analysis, ROC curves, and multivariate logistic regression.

Results: Neuropathic pain was present in 44% of stage 3–4 and 73% of stage 5D patients. PainDETECT scores were significantly higher in stage 5D ($p=0.009$) and showed moderate positive correlations with IL-6 ($r=0.642$, $p<0.001$) and CRP ($r=0.354$, $p=0.001$). ROC analysis identified IL-6 as a strong predictor of neuropathic pain (AUC: 0.808, cut-off: 8.5 pg/mL), while CRP showed lower predictive ability (AUC: 0.658). IL-6 was the only independent predictor in multivariate analysis (OR: 1.155, $p=0.005$). Although HbA1c was not associated with neuropathic pain, diabetes duration showed a strong correlation with PainDETECT scores in diabetic patients.

Conclusion: Elevated IL-6 is significantly associated with neuropathic pain in CKD, particularly in pre-dialysis patients. IL-6 may be a more reliable biomarker than CRP, highlighting the role of systemic inflammation in CKD-related neuropathy.

Keywords: Neuropathic pain, Chronic kidney disease, interleukin-6, C-reactive protein, PainDETECT questionnaire

DOI: 10.5798/dicletip.1906414

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Evre 3-4 ve Evre 5 Kronik Böbrek Hastalığı Olan Hastalarda Nöropatik Ağrı ile Serum İnterlökin-6 ve C-Reaktif Protein Düzeyleri Arasındaki İlişki

Öz

Giriş: Kronik böbrek hastalığı (KBH), sıklıkla periferik nöropati ile ilişkilidir; ancak altta yatan patofizyolojik mekanizmalar tam olarak açıklığa kavuşmamıştır. İnflamatuvar belirteçler, özellikle interlökin-6 (IL-6) ve C-reaktif protein (CRP), nöropatik ağrının gelişimi ve devamında rol oynayabilir. Bu çalışmanın amacı, evre 3–5 KBH hastalarında nöropatik ağrı ile serum IL-6 ve CRP düzeyleri arasındaki ilişkiyi değerlendirmektir.

Yöntemler: Bu prospektif, tek merkezli çalışmaya evre 3–4 KBH'li 40 hasta ile diyalize giren evre 5 (5D) KBH'li 40 hasta olmak üzere toplam 80 hasta dahil edildi. Nöropatik ağrı değerlendirmesi PainDETECT anketi ile yapıldı. Serum IL-6 ve CRP düzeyleri ölçüldü; bu biyobelirteçlerin nöropatik ağrı ile ilişkileri korelasyon analizi, ROC eğrisi ve çok değişkenli lojistik regresyon yöntemleriyle analiz edildi.

Bulgular: Nöropatik ağrı, evre 3–4 hastalarda %44, evre 5D hastalarda ise %73 oranında saptandı. PainDETECT skorları evre 5D hastalarda anlamlı olarak daha yüksekti (p=0,009) ve IL-6 (r=0,642, p<0,001) ile CRP (r=0,354, p=0,001) düzeyleriyle orta düzeyde pozitif korelasyon gösterdi. ROC analizinde IL-6, nöropatik ağrıyı öngörmede güçlü bir belirteç olarak tanımlandı (AUC: 0,808; cut-off: 8,5 pg/mL). CRP'nin öngörü gücü daha düşüktü (AUC: 0,658). Çok değişkenli analizde yalnızca IL-6 bağımsız bir prediktör olarak saptandı (OR: 1,155; p=0,005). HbA1c ile nöropatik ağrı arasında anlamlı ilişki bulunmazken, diyabet süresi ile PainDETECT skorları arasında güçlü bir korelasyon mevcuttu.

Sonuç: Serum IL-6 düzeyindeki artış, özellikle diyaliz öncesi KBH hastalarında nöropatik ağrı ile anlamlı şekilde ilişkilidir. IL-6, CRP'ye kıyasla daha duyarlı ve özgül bir biyobelirteç olabilir. Bu bulgular, KBH'ye bağlı nöropatide sistemik inflamasyonun önemli rolünü ve IL-6'nın klinik bir belirteç olarak potansiyel değerini ortaya koymaktadır.

Anahtar kelimeler: Nöropatik Ağrı, Kronik Böbrek Hastalığı, İnterlökin-6, C-Reaktif Protein, PainDETECT anketi.

INTRODUCTION

Chronic kidney disease (CKD) represents a significant global health concern, as the prevalence of end-stage kidney disease (ESKD) continues to increase across the world[1]. Peripheral neuropathy, a common and disabling manifestation of CKD, is acknowledged as an important contributor to lower limb ulceration and potential amputation[2]. Emerging evidence suggests that peripheral neuropathy may develop during the early stages of CKD, irrespective of diabetes status[2,3]. Uremic neuropathy typically presents with sensory disturbances such as tingling, burning, or paresthesia, primarily affecting the distal lower limbs[4].

In recent years, growing attention has been directed toward the contribution of inflammatory processes to the initiation and persistence of neuropathic pain[5,6]. Multiple investigations have identified changes in inflammatory mediators, including tumor necrosis factor (TNF), interleukin-6 (IL-6), IL-1β, IL-4, and IL-10, among individuals experiencing neuropathic pain[7]. The synthesis of IL-6 is mainly triggered by IL-1β and TNF-α and is upregulated as part of the inflammatory cascade following infection or tissue injury[8]. Its secretion is stimulated during the inflammatory response following tissue injury or infection. After being released, IL-6 circulates through the bloodstream to the liver, where it induces hepatic production of C-reactive protein (CRP)[9]. Elevated levels of these biomarkers contribute to the maintenance of pain and may alter neuronal function, thereby promoting the development of neuropathic pain[10]. The PainDETECT questionnaire is widely utilized as a validated screening instrument to identify patients potentially exhibiting neuropathic pain[11]. Developed to evaluate neuropathic characteristics of pain, this instrument has proven effective in reliably differentiating pain

intensity among CKD patients[12]. The aim of our study is to investigate the relationship between neuropathic pain and serum IL-6 and CRP levels in patients with chronic kidney disease.

METHODS

Study Design and Participants

This prospective observational study was carried out between February and May 2024, enrolling 248 individuals diagnosed with stage 3–4 CKD or stage 5D CKD (receiving dialysis) who were being followed in our nephrology outpatient department. Among these, 134 participants declined to complete the neuropathic pain questionnaire, while 34 were excluded because of missing biochemical parameters. Consequently, 80 participants were included in the final statistical evaluation. The exclusion criteria included patients younger than 18 years or older than 75 years, as well as those with vitamin B12 deficiency, active infections, systemic inflammatory or neurological diseases, significant alcohol consumption, or other known causes of peripheral neuropathy. In addition, patients with active infections or conditions known to affect inflammatory biomarkers were excluded at baseline. All participants provided written informed consent after receiving a comprehensive explanation of the study's aims and procedures.

Pain Assessment Tool

The PainDETECT questionnaire, a validated self-administered tool for detecting neuropathic pain components, was used for pain assessment. Patients with stage 3–4 CKD completed the questionnaire during routine outpatient visits, while stage 5D patients were assessed post-dialysis.

The PainDETECT consists of four components: (1) three 11-point Likert items evaluating current, average, and maximum pain intensity over the past four weeks; (2) a pain pattern item with four graphical descriptors scored from −1 to +1; (3) a body map assessing radiation of pain (scored +2 if present); and (4) seven items evaluating the quality of sensory symptoms, each scored on a 0–5 Likert scale. The total score ranges from 0 to 38. A score ≤12 indicates an unlikely neuropathic pain component, ≥19 indicates a high probability, and scores between 13–18 are considered ambiguous[13].

Biochemical Evaluation

In addition to routine laboratory tests (complete blood count, creatinine, BUN, sodium, potassium, calcium, phosphorus, and CRP), serum IL-6 levels were measured. While collecting routine samples, an additional 5 mL of venous blood was drawn into gel tubes for IL-6 analysis. Samples were centrifuged at 10,000 rpm for 10 minutes to separate plasma, which was then aliquoted into 500 µL Eppendorf tubes, labeled, and stored at –80°C.

Data Collection and Statistical Analysis

Information on demographic characteristics (including age, sex, height, and weight), comorbidities, medication use, and laboratory findings was extracted from electronic medical records. Statistical analyses were carried out using IBM SPSS Statistics, version 26.0. Descriptive variables were summarized as counts and percentages for categorical data, and as mean ± standard deviation or median (interquartile range, IQR) for continuous data. Group comparisons were evaluated using the Chi-square test or Fisher's exact test for categorical variables, and either the independent samples t-test or Mann–Whitney U test for continuous variables, where applicable. The association between PainDETECT scores and serum IL-6, CRP, and HbA1c values was analyzed using Spearman's rank correlation.

Predictive and Regression Analyses

The discriminative ability of serum IL-6 and CRP in predicting neuropathic pain was assessed

using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) and corresponding 95% confidence intervals (CIs) were computed. Optimal threshold values were established according to the Youden index, considering both sensitivity and specificity parameters.

To explore independent predictors of neuropathic pain, logistic regression analyses were conducted. Variables demonstrating a significance level of $p < 0.25$ in the univariate phase were entered into a multivariate logistic regression model, applying the backward likelihood ratio approach. The variables included in the multivariate model were CRP (mg/L), sodium (mEq/L), potassium (mEq/L), magnesium (mEq/L), HbA1c, and CKD stage. Model adequacy was evaluated using the Hosmer–Lemeshow goodness-of-fit test, which demonstrated acceptable model calibration. A two-tailed p value < 0.05 was regarded as the criterion for statistical significance. The study was approved by the Gazi University Ethics Committee (Decision No: 1041, Date: 25.12.2023).

RESULTS

A total of 80 patients were enrolled in the study, comprising stage 3 (n=26), stage 4 (n=14), and stage 5D CKD (n=40). Half of the participants were female (n=40), 25% (n=20) were university graduates, 73.8% (n=59) were current smokers, and 5% (n=4) reported alcohol consumption. The mean age was 50.5 ± 11.9 years, and the mean BMI was 24.6 ± 3.5 kg/m^2. A history of hypertension (HT) was observed in 80% (n=64), diabetes mellitus (DM) in 38.8% (n=31), and coronary artery disease (CAD) in 43.8% (n=35) of patients. HT and DM were identified as the primary etiologies of CKD in 37.5% (n=30) and 28.8% (n=23) of the cases, respectively. The mean systolic and diastolic blood pressures were 124 ± 23 mmHg and 75 ± 13 mmHg, respectively. Further details are provided in table I.

Table I: Demographic and Clinical Characteristics of the Study Population

Variable	**Value (n=80)**	
	n	**%**
Gender		
Female	40	50.0
Male	40	50.0
Educational Status		
Primary School	34	42.5
High School	26	32.5
University	20	25.0
Smoking		
Smoker	21	26.3
Non-smoker	59	73.8
Alcohol Consumption		
Yes	4	5.0
No	76	95.0
Hypertension		
Present	64	80.0
Absent	16	20.0
Diabetes Mellitus		
Present	31	38.8
Absent	49	61.3
Hyperlipidemia		
Present	29	36.3
Absent	51	63.8
Coronary Artery Disease		
Present	35	43.8
Absent	45	56.3
Etiology of Chronic Kidney Disease		
Diabetes Mellitus	23	28.8
Hypertension	30	37.5
Glomerulonephritis	18	22.5
Others	9	11.2
Age (years) (mean ± SD)	50.5±11.9	
BMİ (kg/m^2) (mean ± SD)	24.6±3.5	
Systolic/ Diastolic Blood Pressure (mmHg) (mean ± SD)	124±23/75±13	
Duration of Dialysis (years)	6.5 (4-12)	

* median (interquartile range), BMI: Body Mass Index

When comparing stage 3–4 CKD and stage 5D CKD patients, statistically significant differences were found in neuropathic pain scores (p=0.009), IL-6 (p=0.004), phosphorus (p=0.010), age (p=0.003), and magnesium (p=0.009), all of which showed a positive correlation with disease stage. In contrast, hemoglobin (p=0.010), neutrophil count (p=0.004), lymphocyte count (p=0.049), potassium (p<0.001), and calcium levels (p<0.001) were negatively associated with CKD stage (Table II). In addition, PainDETECT scores demonstrated a stepwise increase with advancing CKD stage, indicating a positive association between disease severity and neuropathic pain burden.

Table II: Comparison of Demographic Data, Clinical Characteristics, and Laboratory Results Between Stage 3–4 CKD Patients and Stage 5D CKD Patients

	STAGE 3-4 n=40		**STAGE 5D n=40**		**p#**
	Mean	**SD**	**Mean**	**SD**	
PainDETECT	15.4	8.3	20.2	8.1	**0.009**
IL–6 (pg/mL)*	6.9 (3.8-12.2)		10.8 (7.8-19.0)		**0.004***
CRP (mg/L)*	5.0 (2.5-9.7)		5.4 (2.4-12.3)		0.580*
Hemoglobin (g/dL)	12.6	1.8	11.6	1.3	**0.010**
Neutrophil (µL)	5250	2032	4098	1315	**0.004**
Lymphocyte (µL)	1720	792	1435	423	**0.049**
Sodium (mEq/L)	138.9	3.4	138.1	2.6	0.226
Potassium (mEq/L)	4.4	0.6	3.6	0.4	**<0.001**
Calcium (mEq/L)	9.2	0.7	8.4	0.5	**<0.001**
Magnesium (mEq/L)	2.0	0.3	2.1	0.3	**0.009**
Phosphorus (mEq/L)	4.0	1.2	4.6	1.0	**0.010**
Chloride (mEq/L)	103.6	5.6	101.4	3.9	0.054
HbA1c	5.9	0.9	6.1	1.0	0.314
Age (years)	46.6	11.8	54.4	10.8	**0.003**
Gender, Male n (%)	20 (50.0)		20 (50.0)		1.0&
Female n (%)	20 (50.0)		20 (50.0)		

Compared to CKD patients without neuropathic pain, those with neuropathic pain had significantly higher levels of IL-6 (p<0.001), CRP (p=0.021), HbA1c (p=0.012), and more advanced CKD stages (p=0.013) (Table III).

Table III: Comparison of Demographic Data, Clinical Characteristics, and Laboratory Results Between CKD Patients with and Without Neuropathic Pain

	NEUROPATHİC PAİN				**p#**
	PRESENT n=44		**ABSENT n=31**		
	Mean	**SD**	**Mean**	**SD**	
IL–6 (pg/mL)*	12.4 (8.9-21.8)		5.4 (3.6-9.3)		**<0.001***
CRP (mg/L)*	6.5 (3.0-13.7)		3.0 (2.0-10.0)		**0.021***
Hemoglobin (g/dL)	11.9	1.5	12.1	1.6	0.646
Neutrophil (µL)	4430	1508	4935	2147	0,264
Sodium (mEq/L)	138.0	2.7	139.1	3.5	0.129
Potassium (mEq/L)	3.9	0.6	4.2	0.7	0.050
Calcium (mEq/L)	8.7	0.7	8.9	0.7	0.339
Magnesium (mEq/L)	2.1	0.3	2.0	0.3	0.163
HbA1c	6.1	1.1	5.9	0.8	**0.012**
Age (years)	53.4	11.1	46.5	12.3	0.646
GFR (mL/min/1.73 m²)*	11.0 (8.3-39.3)		27.0 (9.0-47.0)		0.082
Gender Male n (%)	22 (59.5)		15 (40.5)		0.891&
Female n (%)	22 (57.9)		16 (42.1)		
Stage 3-4 n (%)	17 (44.7)		21 (55.3)		**0.013**&
5D n (%)	27 (73.0)		10 (27.0)		

In patients with stage 5D CKD, the median duration of dialysis was 6.5 years (interquartile range: 4–12 years). Additional analyses revealed no significant association between dialysis duration and either the presence of neuropathic pain or PainDETECT scores (p>0.05).

Among stage 3–4 CKD patients, PainDETECT scores were moderately and positively correlated with IL-6 (r=0.583, p<0.001) and CRP (r=0.378, p=0.016). In stage 5D CKD patients, a similar correlation was observed between PainDETECT scores and IL-6 (r=0.608, p<0.001). When analyzing all CKD patients collectively, PainDETECT scores showed a moderate and significant positive correlation with IL-6 (r=0.642, p<0.001) and CRP (r=0.354, p=0.001) (Table IV). However, no significant correlation was found between PainDETECT scores and HbA1c levels (p>0.05) (Table V).

Table IV: Correlation of PainDETECT Score with IL-6 and CRP Levels in CKD Patients (Stages 3–4, Stage 5D, and Total)

		PainDETECT Score		
		Stage 3-4 n=40	**Stage 5D n=40**	**Total n=80**
IL-6	r*	**0.583**	**0.608**	**0.642**
	p	**<0.001**	**<0.001**	**<0.001**
CRP	r*	**0.378**	0.308	**0.354**
	p	**0.016**	0.053	**0.001**

** Spearman correlation coefficient*

Table V: Correlation Between PainDETECT Score and HbA1c Levels in CKD Patients (Stages 3, 4, 5D, and Overall)

		PainDETECT Score			
		Stage 3 n=26	**Stage 4 n=14**	**Stage 5D n=40**	**Total n=80**
HbA1c	r*	0.377	-0.282	-0.064	0.071
	p	0.058	0.329	0.694	0.534

In stage 5D CKD patients, PainDETECT scores demonstrated a strong positive correlation with diabetes duration (r=0.862, p<0.001). When considering all diabetic CKD patients (n=31), a

moderate positive correlation was also observed (r=0.697, p<0.001) (Table VI).

Table VI: Correlation Between PainDETECT Score and Duration of Diabetes in CKD Patients (Stages 3, 4, 5D, and Overall)

		PainDETECT Score			
		Stage 3 n=8	**Stage 4 n=5**	**Stage 5D n=18**	**Total n=31**
Duration of Diabetes	r*	0.512	0.051	**0.862**	**0.697**
	p	0.195	0.935	**<0.001**	**<0.001**

A statistically significant difference in neuropathic pain prevalence was found between patients with normal and elevated IL-6 levels, both in stage 3–4 CKD patients (p=0.001) and in the overall CKD cohort (p<0.001) (Table VII). However, no such association was found for CRP levels (p=0.082) (Table VIII).

Table VII: Comparison of Patients with Normal and Elevated IL-6 Levels in Terms of the Presence of Neuropathic Pain

		Normal n=26		**Elevated n=49**		**p**
CKD	**Neuropathic Pain**	**n**	**%**	**n**	**%**	
Stage 3-4	Present	3	16.7	14	70.0	**0.001**#
	Absent	15	83.3	6	30.0	
Stage 5D	Present	4	50.0	23	79.3	0.174*
	Absent	4	50.0	6	20.7	
Total	Present	7	26.9	37	75.5	**<0.001**#
	Absent	19	73.1	12	24.5	

*#Chi-square test, *Fisher's exact test*

Table VIII: Comparison of Patients with Normal and Elevated CRP Levels in Terms of the Presence of Neuropathic Pain

		Normal n=37		**Elevated n=38**		**p**
CKD	**Neuropathic Pain**	**n**	**%**	**n**	**%**	
Stage 3-4	Present	6	31.6	11	57.9	0.103#
	Absent	13	68.4	8	42.1	
Stage 5D	Present	12	66.7	15	78.9	0.476*
	Absent	6	33.3	4	21.1	
Total	Present	18	48.6	26	68.4	0.082#
	Absent	19	51.4	12	31.6	

*#Chi-square test, *Fisher's exact test*

Receiver operating characteristic (ROC) curve analysis revealed that IL-6 was a good predictor of neuropathic pain, with an AUC of 0.808 (95% CI: 0.706–0.909, p<0.001). The optimal cutoff value was determined as 8.5 pg/mL (Figure I).

CRP showed a moderate predictive capacity with an AUC of 0.658 (95% CI: 0.532–0.784, p=0.021), and the optimal cutoff value was 4.3 mg/L (Figure II).

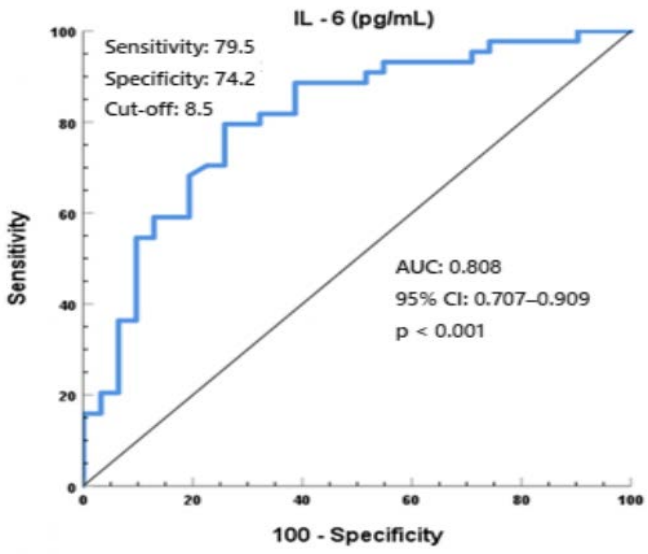

Figure 1. ROC curve for predicting the presence of neuropathic pain based on IL-6 levels

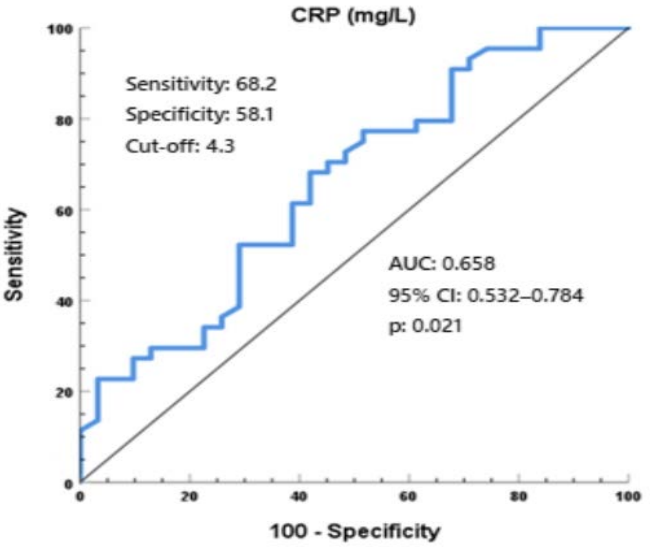

Figure 2. ROC curve for predicting the presence of neuropathic pain based on CRP levels

In the logistic regression analysis including 44 patients with and 31 patients without neuropathic pain, variables with p<0.25 in univariate analysis were entered into the multivariate model using the backward likelihood ratio method. Among the predictors, only IL-6 remained statistically significant. Each 1 pg/mL increase in IL-6 was associated with a 1.155-fold increase in the odds of having neuropathic pain (95% CI: 1.045–1.278, p<0.001) (Table IX).

Table IX: Evaluation of Neuropathic Pain Risk Factors in Patients with Chronic Kidney Disease (CKD) Included in the Study Using Logistic Regression Analysis

Variable	β	OR	%95 C.I	p
IL – 6 (pg/mL)	0.145	1.155	1.045-1.278	**0.005**

Independent Variables Evaluated in Model Formation: CRP (mg/L), Sodium (mEq/L), Potassium (mEq/L), Magnesium (mEq/L), HbA1c, and CKD Stage.

DISCUSSION

This investigation explored the association between serum IL-6, CRP, and neuropathic pain among individuals with stage 3–4 and stage 5 CKD. Significant correlations were identified between PainDETECT scores and both IL-6 and CRP concentrations in patients with stage 3–4 CKD, whereas in stage 5D patients, a notable association persisted only between PainDETECT scores and IL-6 levels. Although IL-6 emerged as an independent predictor of neuropathic pain, the observational design of the study does not allow causal inferences. Prospective mechanistic and interventional studies are warranted to further elucidate this relationship.

Over the last three decades, the global burden of CKD has increased substantially, now affecting nearly 13% of the world's population[14,15]. Peripheral neuropathy represents one of the most prevalent yet often overlooked complications of CKD[16]. The underlying mechanisms are believed to involve uremic toxicity, inflammatory pathways, and oxidative stress[17]. In contrast to nociceptive pain, neuropathic pain is generally characterized by burning sensations, tingling, and other sensory disturbances[18], which has led to the creation of several screening instruments designed to detect neuropathic pain components[19]. One such instrument, the PainDETECT questionnaire, was originally introduced in 2004 by the German Research Network on Neuropathic Pain, and its Turkish validation was later completed by Alkan et al. in 2013 13. It was chosen for this study due to its strong

psychometric properties, including a reported sensitivity of 85% and specificity of 95%[20].

In our cohort, neuropathic pain was identified in 44% of stage 3–4 CKD patients and 73% of stage 5D patients. In a study by Pasaylo et al. involving 169 HD patients, 35% were found to have neuropathic pain using the PainDETECT questionnaire, and these patients had significantly lower quality of life scores[21]. The higher prevalence in our study may be attributed to differences in pain thresholds and the underlying etiologies of CKD among the enrolled population.

PainDETECT scores were significantly higher in stage 5D patients compared to those in stages 3–4. This finding aligns with the results of a recent study by Chiu et al., who reported an increased prevalence of peripheral neuropathy in advanced CKD stages[22]. The greater burden of chronic inflammation and accumulation of uremic toxins in later stages may explain the higher frequency of neuropathic pain in these patients.

Elevated IL-6 levels have been previously linked to neuropathic pain. Chanda et al. reported higher IL-6 levels in diabetic patients with neuropathy compared to those without[23], and Herder et al. observed significantly elevated IL-6 levels in patients with painful distal sensorimotor polyneuropathy[24]. Panichi et al. demonstrated a negative correlation between IL-6/CRP levels and creatinine clearance in stable pre-dialysis patients[25]. Similarly, Doupis et al. found significantly higher CRP levels in diabetic patients with neuropathy than in those without[26]. Consistent with these findings, our study demonstrated a significant correlation between PainDETECT scores and both IL-6 and CRP levels, suggesting that elevated IL-6 and CRP may contribute to neuropathy through inflammatory mechanisms.

Although the mean HbA1c level in our cohort was 5.97 ± 0.96%, no significant relationship was found between HbA1c and neuropathic pain. This contrasts with findings by Baxi et al., who reported an increased likelihood of painful peripheral neuropathy in diabetic patients with HbA1c levels above 9%[27]. In contrast, Naranjo et al. found no significant association between HbA1c and neuropathic pain in patients with a mean HbA1c of 7.46 ± 1.34%[28]. The absence of a relationship in our study may be due to the overall lower HbA1c levels in our population, likely influenced by decreased insulin requirements and better glycemic control in CKD.

Furthermore, we identified a strong positive correlation between diabetes duration and PainDETECT scores in stage 5D patients, and a moderate correlation in all diabetic CKD patients. These findings are consistent with those of Nisar et al., who found a higher prevalence of neuropathy in patients with diabetes duration longer than three years[29]. Prolonged hyperglycemia may contribute to neuropathic pain through mechanisms such as oxidative stress and the accumulation of advanced glycation end products.

Inflammatory mediators released in chronic systemic inflammation may sensitize peripheral nociceptors, thereby promoting pain perception[30]. In our study, IL-6 demonstrated greater sensitivity and specificity than CRP in predicting neuropathic pain. IL-6 may play a more central role by modulating neuronal excitability and acting as a key regulator of acute-phase protein synthesis. It may thus serve as a more robust inflammatory biomarker in CKD-associated neuropathic pain.

A distinguishing feature of our study is the stratification of CKD patients into stage 3–4 and stage 5 groups to assess the association between neuropathic pain and inflammatory markers. ROC analysis showed that IL-6 levels could predict neuropathic pain across both groups. Notably, IL-6 appeared to be a more

valuable predictor in pre-dialysis patients compared to those on dialysis.

This study has several limitations. It was conducted in a single center with a relatively small sample size. Therefore, the relatively small sample size and single-center design may limit the generalizability of our findings. Although we aimed to explore the relationship between neuropathic pain and inflammatory markers in CKD, common confounders such as diabetes and other neuropathy-related disorders were not excluded, which may have influenced the findings. In addition, although a high proportion of patients were smokers, the potential confounding effect of smoking on neuropathic pain was not specifically analyzed and should be considered in future studies.

CONCLUSION

This study highlights a significant association between elevated serum IL-6 levels and the presence of neuropathic pain in patients with CKD, particularly among those in the pre-dialysis stages. While both IL-6 and CRP were correlated with neuropathic pain, IL-6 demonstrated superior predictive power and was identified as the only independent biomarker in multivariate analysis. These findings support the role of systemic inflammation in the pathogenesis of CKD-related neuropathy and underscore IL-6 as a potentially valuable clinical marker for identifying high-risk patients. Further multicenter studies with larger sample sizes are warranted to validate these results and explore the therapeutic implications of targeting inflammation in the management of neuropathic pain in CKD.

Ethical approval: The study was approved by the Gazi University Ethics Committee (Decision No: 1041, Date: 25.12.2023).

Conflict of Interest: The authors declared no conflicts of interest.

Financial Disclosure: The authors declared that this study has receivet no financial support.

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