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Analysis of Factors Affecting Disease Progress and Mortality in Patients with Chronic Renal Disease

Kronik Böbrek Hastalığı Olan Hastalarda Hastalık Progresyonuna ve Mortaliteye Etki Eden Faktörlerin Analizi

ABSTRACT

Objective:

To investigate the variables influencing disease progression and death in chronic renal disease patients (CKD).

Material and Methods:

The design of this retrospective cohort study was conducted on patients who were referred to the Nephrology Outpatient Clinic with a Glomerular Filtration Rate (GFR) <60 ml/min/1.73 m² in the emergency department and other outpatient clinics of a tertiary hospital between 2009 and 2016. A GFR decline rate of ≥5 ml/min/year was defined as "rapidly progressive" CKD and <5 ml/min/year as "slowly progressive" CKD. The endpoints were renal replacement therapy admission and death.

Results:

The research comprised 737 patients, with 464 (63%) of them being men. The average duration of follow-up was 16.87 ± 18.55 months. Using the renin-angiotensin-aldosterone system (RAAS) blockers and hyperphosphatemia increased the rate of progression of renal disease. The presence of coronary artery disease and high proteinuria levels increased the hazard of renal replacement therapy (RRT) initiation, whereas statin and vitamin D use decreased this risk. Furthermore, the presence of heart failure, hyperphosphatemia, and anemia raised the risk of death but using RAAS blockers, vitamin D, and high albumin levels lowered the risk of mortality.

Conclusion:

CKD is a chronic illness with a significant morbidity and death rate. Recognizing and treating the factors that cause the progression of this disease will improve patient survival.

Key Words:

Chronic Kidney Disease, Progression, Mortality

ÖZ

Amaç:

Kronik böbrek hastalığı hastalarında (KBH) hastalık progresyonu ve ölümü etkileyen değişkenleri araştırmak.

Gereç ve Yöntemler:

Bu retrospektif kohort çalışması, 2009 ve 2016 yılları arasında üçüncü basamak hastanenin acil servis ve diğer polikliniklerinde Glomerüler Filtrasyon Hızı (GFR) <60 ml/dk/1.73 m² ile Nefroloji Polikliniğine sevk edilen hastalar üzerinde yapılmıştır. ≥5 ml/dk/yıllık bir GFR düşüş oranı "hızlı ilerleyen" KBH ve <5 ml/dk/yıl "yavaş ilerleyen" KBH olarak tanımlandı. Son noktalar renal replasman tedavisine kabul ve ölümdü.

Bulgular:

Araştırmaya 464'ü (%63) erkek olmak üzere 737 hasta dahil edildi. Ortalama takip süresi 16,7 ± 18,55 aydı. Renin-anjiyotensin-aldosteron system (RAAS) blokerleri ve hiperfosfatemi kullanımı böbrek hastalığının ilerleme hızını artırdı. Koroner arter hastalığı ve yüksek proteinüri düzeylerinin varlığı renal replasman tedavisi (RRT) başlama riskini artırırken, statin ve D vitamini kullanımı bu riski azalttı. Ayrıca, kalp yetmezliği, hiperfosfatemi ve anemi varlığı ölüm riskini artırdı, ancak RAAS blokerleri, D vitamini ve yüksek albümin düzeylerinin kullanılması ölüm riskini azalttı.

Sonuç:

KBH, önemli bir morbidite ve ölüm oranına sahip kronik bir hastalıktır. Bu hastalığın ilerlemesine neden olan faktörlerin tanınması ve tedavi edilmesi hasta sağkalımını iyileştirecektir.

Anahtar Sözcükler:

Kronik Böbrek Hastalığı, İlerleme, Mortalite

INTRODUCTION

Persistent kidney disease is defined by the chronic, progressive, and irreversible loss of nephrons caused by a variety of factors. It is defined as objective kidney damage that lasts at least 3 months regardless of the underlying renal disease's etiology and/or a drop in glomerular filtration rate (GFR) below 60 ml/min/1.73 m2 (1-3). Because of its growing global prevalence, it has become a significant public health issue (4). This indicates that the number of patients with chronic renal failure admitted to emergency departments, and internal medicine outpatient clinics would rise. The disease progresses due to its progressive nature, and patients require renal replacement therapies (RRT) such as dialysis or transplantation due to developing end-stage renal disease (ESRD) (5). These renal replacement therapies have prolonged the survival of patients (5). This disease, which is a significant source of morbidity and mortality, also causes a significant increase in health expenditures due to severe labor loss and high treatment costs. Slowing the course of chronic renal disease has been the primary objective of therapy for all of these reasons.Chronic renal disease's primary causes are diabetes mellitus, hypertension and chronic glomerulonephritis. Depending on the etiology of kidney disease, the rate of progression can vary. In addition to factors with known adverse effects such as diabetes, hypertension, proteinuria, anemia, age, gender, ethnicity, obesity, smoking and medications used, it is probable that there are reasons that have not been fully revealed that affect the rate of progression of the disease (5-8). Identifying and treating high-risk individuals by understanding the variables that contribute to the course of renal disease can help minimize the morbidity and mortality associated with this illness (8). The goal of this study was to see how demographic, clinical, and treatment-related factors, as well as laboratory data, affected the rate of disease progression and death in people with chronic kidney disease.

MATERIAL and METHODS

Study design and settings

This article was produced from the specialty thesis of Dr. Selami BAYRAM, under the supervision of Prof. Dr. Gultekin SULEYMANLAR, at Akdeniz University Hospital, Department of Internal Diseases. This retrospective cohort study design was conducted at the Hospital of the University Faculty of Medicine, a Tertiary Care Hospital, between 2009 and 2016. The University Faculty of Medicine Clinical Research Ethics Committee authorized the study and waived the necessity for informed consent. (Decision number:8 date:06th January 2016). The present study was conducted in accordance with the research and publication ethics of the Declaration of Helsinki. Patients who were confirmed to have a GFR level of <60 ml/min/1.73 m² in the emergency department and other outpatient clinics were referred to the Department of Internal Medicine, Division of Nephrology Outpatient Clinic. The age, gender, admission dates, diabetes, hypertension, coronary artery disease, and congestive heart failure inpatient data was pulled from the hospital registry system and were all documented. Additionally; serum glucose, BUN, creatinine, GFR, ALT, ALP, sodium, potassium, calcium, phosphorus, parathormone (PTH), uric acid, albumin, low-density lipoprotein (LDL), triglyceride, hemoglobin, bicarbonate, HbA1c, ferritin at baseline and final controls, sedimentation and proteinuria levels, angiotensin converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB), vitamin D, erythropoietin stimulating agent, allopurinol, statin and acetylsalicylic acid use of the patients were documented. Patients were classified according. Patients were classified according to GFR stage at baseline and compared in terms of clinical, demographic characteristics and laboratory values. Patients were then separated into two groups based on the rate of yearly GFR decrease. A GFR decline rate of ≥5 ml/min/year was defined as "rapidly progressive" CKD and <5 ml/min/year as "slowly progressive" CKD. Clinical, demographic, and treatment variables, as well as laboratory data, were compared between the two groups. In addition, the factors af-

fecting the rate of GFR decline were determined by univariate analysis and supported by multivariate analysis. In our study, renal replacement therapy and death were identified as endpoints. Patients who started renal replacement therapy (RRT) after the start of follow-up and who died were divided into three groups consisting of RRT, death and RRT/death combined endpoints in terms of survival times and factors that may affect this and the groups were analyzed based on demographics, clinical, and laboratory criteria.

Data Analysis

For statistical analysis, SPSS 20.0 was employed. The arithmetic mean and standard deviation of continuous variables were used ($\bar{x}$±sd). Numerical parameters were compared by student-t test; categorical parameters were compared by chi-square and Fischer's Exact test. Pearson's correlation analysis was used to analyze the correlation between the course of CKD and the factors that may affect it. The factors associated with the rate of progression were then backward eliminated and supported by multivariate logistic regression analysis, one of the advanced statistical methods. The Kaplan-Meier technique was used for survival analysis. In addition, factors that may affect the time to RRT initiation, death, and time to RRT/death endpoints were defined by Cox regression analysis. A P value < 0.05 was deemed important.

RESULTS

The study involved 737 patients in total. Of the patients, 464 (63%) were male and 273 (37%) were female. The mean age was 61.02 ± 15.20 years and the mean follow-up period was 16.87 ± 18.55 months. Table I details the demographics, clinical features, treatment characteristics, and laboratory findings of patients grouped according to baseline GFR stage, as well as the statistical significance between the groups.

Table I: Demographic, clinical, and treatment characteristics and laboratory findings of patients classified according to baseline GFR stage

	GFR (mL/min/1.73 m²)				
	<15 (n:118.16%)	15-29 (n:418.56.7%)	30-44 (n:176.23.9%)	≥45 (n:25.3.4%)	p
Age	58.36±14.12	61.54±15.29	61.22±15.56	63.64±15.41	0.285
Gender (%)					**0.005**
Male	60.2	61.2	64.2	96.0	
Female	39.8	38.8	35.8	4.0	
DM (%)	33.1	36.1	39.2	28.0	0.589
HT (%)	83.1	77.5	75.0	72.0	0.368
CAD (%)	5.1	9.3	13.6	12.0	0.104
HF (%)	3.4	9.8	8.0	0.0	0.059
ACEi/ARB (%)	6.8	19.6	26.7	32.0	**< 0.001**
Statin (%)	16.1	29.9	39.2	36.0	**< 0.001**
Vitamin D (%)	34.7	49.5	34.1	20.0	**< 0.001**
EPO (%)	11.0	10.5	4.5	0.0	**0.034**
ASA (%)	19.5	33.0	39.2	36.0	**0.005**
Allopurinol (%)	41.5	62.4	65.9	68.0	**< 0.001**
Creatinine (mg/dl)	4.80±1.44	2.83±0.65	1.92±0.51	1.45±0.16	**0.014**
BUN (mg/dl)	64.11±20.48	46.11±14.58	32.62±9.47	24.20±5.37	0.062
GFR (ml/min)	12.12±3.40	21.75±4.26	34.86±3.74	50.20±4.58	**0.040**
Glucose (mg/dl)	111.55±63.97	115.66±57.77	107.57±36.54	94.13±13.99	0.324
Albumin (g/dl)	4.14±0.50	4.17±0.49	4.33±0.42	4.42±0.38	0.611
ALT (IU/L)	17.96±21.28	18.35±13.40	21.39±20.34	19.94±8.95	0.624
ALP (IU/L)	129.51±76.81	119.04±64.98	139.3±110.76	182.90±83.97	**0.008**
LDL (mg/dl)	121.53±44.09	122.40±42.50	114.49±39.24	102.04±31.31	0.283
Triglycerides (mg/dl)	143.79±65.75	164.93±108.17	175.24±126.76	147.38±70.66	0.644
Sodium (mEq/l)	139.66±5.05	139.95±4.09	140.66±3.39	141.08±2.11	0.227
Potassium (mEq/l)	4.95±0.69	4.98±0.66	4.99±0.67	4.84±0.53	0.133
Calcium (mg/dl)	9.06±0.91	9.22±0.63	9.39±0.51	9.43±0.32	0.650
Phosphorus (mg/dl)	4.81±1.04	4.06±0.77	3.65±0.61	3.29±0.49	0.798
PTH (pg/ml)	303.07±243.62	153.24±104.63	91.19±54.92	87.19±39.46	**0.033**
Hemoglobin (g/dl)	10.81±1.57	11.62±1.66	12.58±1.71	13.67±1.58	0.174
Bicarbonate (mEq/l)	20.21±3.98	21.86±4.39	23.30±3.94	24.79±2.94	0.262
Uric acid (mg/dl)	6.98±1.70	7.16±1.93	6.85±1.81	6.99±1.53	0.509
Ferritin (ng/ml)	240.27±305.90	183.55±176.37	133.44±133.41	91.42±81.04	0.159
Sedimentation (mm/s)	43.89±33.94	43.23±25.11	33.36±25.73	27.00±20.71	0.657
HbA1C (%)	6.57±1.71	6.83±1.81	7.02±1.66	6.30±1.37	0.281
25 (OH) D3 (ng/ml)	15.73±17.97	16.98±12.77	24.43±17.94	24.15±6.85	0.113
Proteinuria (g/day)	2.59±2.62	1.64±2.14	1.05±1.63	0.53±1.06	0.804

Note: Values are expressed as $\bar{X}$ ± SD and percentage (%), DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, HF: heart failure, PTH: parathormone. ACEi/ARB: Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker, LDL: low-density lipoprotein, Hgb: hemoglobin, EPO: erythropoietin, ASA: acetylsalicylic acid.

Table II details the demographic, clinical, therapeutic features, and laboratory findings of patients grouped according to GFR stage at the last follow-up visits, as well as the statistical significance between the groups.

The demographic, clinical, treatment characteristics and laboratory findings of the groups formed according to the annual GFR decline rate of the patients and the statistical significance between these two groups are shown in detail in Table III.

Table II: Demographic, clinical, treatment and laboratory findings of the patients classified according to GFR stage at the last follow-up visit

	GFR (mL/min/1.73 m²)				
	<15 (n:261 35.4%)	15-29 (n:291 39.5%)	30-44 (n:137 18.6%)	≥45 (n:48 6.5%)	p
Age	56.50±14.89	63.07±14.76	63.89±15.75	65.02±12.22	0.498
Gender (%)					0.749
Male	62.5	61.5	65.0	68.8	
Female	37.5	38.5	35.0	31.2	
DM (%)	34.1	40.5	35.8	54.2	**0.045**
HT (%)	77.4	77.3	76.6	83.3	0.801
CAD (%)	8.4	8.2	13.1	16.7	0.130
HF (%)	5.0	9.3	9.5	12.5	0.132
ACEi/ARB (%)	9.2	19.9	34.3	33.3	**<0.001**
Statin (%)	22.6	31.6	40.1	33.3	**0.003**
Vitamin D (%)	38.7	52.6	33.6	27.1	**<0.001**
EPO (%)	14.6	6.5	4.4	4.2	**0.001**
ASA (%)	23.8	35.4	38.7	43.8	**0.002**
Allopurinol (%)	49.4	67.0	65.0	62.5	**<0.001**
Creatinine (mg/dl)	5.78±2.03022	2.83±.84141	1.84±.57914	1.42±.81	**<0.001**
BUN (mg/dl)	73.85±23.96	47.87±16.33	32.64±9.49	23.02±5.94	**<0.001**
GFR (ml/min)	10.16±2.72	21.51±4.22	36.16±4.04	53.18±7.97	**<0.001**
Glucose (mg/dl)	105.66±43.86	110.37±51.11	104.38±34.92	116.02±43.88	0.618
Albumin (g/dl)	4.06±0.52	4.13±0.44	4.26±0.35	4.40±0.33	**0.001**
ALT (IU/L)	16.18±15.73	17.26±17.24	19.08±12.96	27±28.38	0.998
ALP (IU/L)	102.54±52.4	109.44±91.3	110.79±88.83	100.17±58.92	0.479
LDL (mg/dl)	111.19±38.41	108.11±34.16	104.26±33.46	104.50±29.70	0.911
Triglycerides (mg/dl)	140.23±79.97	147.37±76.31	160.23±123.64	159.21±89.88	0.103
Sodium (mEq/l)	138.83±4.55	139.12±4.05	140.05±4	140.95±3.84	0.335
Potassium (mEq/l)	4.76±.673	4.79±.579	4.81±.544	4.74±.45	0.975
Calcium (mg/dl)	8.94±0.9	9.19±0.6	9.4±0.54	9.50±.51	**<0.001**
Phosphorus (mg/dl)	5.08±1.3	3.9533±0.7	3.4910±0.6	3.33±0.54	**<0.001**
PTH (pg/ml)	267.93±212.07	144.67±120.77	100.7±65.45	83.92±50.20	**<0.001**
Hemoglobin (g/dl)	10.73±1.52	11.8±1.65	12.65±1.63	13.33±1.67	**<0.001**
HCO3 (mEq/l)	21.18±4.42	23.36±5.14	24.77±4.19	25.6±4.23	0.171
Uric acid (mg/dl)	6.72±1.58	6.65±1.67	6.65±1.49	6.41±1.35	0.974
Ferritin (ng/ml)	205.15±201.99	179.32±266.45	124.81±126.72	109.01±128.57	**0.001**
Sedimentation (mm/s)	37.41±25.34	36.2±23.63	30±23.8	27.02±18.51	**<0.001**
HbA1C (%)	6.27±1.91	6.55±1.89	6.34±1.38	6.48±1.31	0.122
25 (OH) D3 (ng/ml)	14.33±15.72	17.47±14.29	21.69±14.1	22.34±12.38	**0.015**
Proteinuria (g/day)	3.09±3	1.65±2.07	0.6±.93	0.41±1.24	**<0.001**

Note: Values are expressed as $\bar{X}$±SD and percentage (%), DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, HF: heart failure, PTH: parathormone. ACEi/ARB: Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker, LDL: low density lipoprotein, Hgb: hemoglobin, EPO: erythropoietin, ASA: acetyl salicylic acid, ALP: alkaline phosphatase, ALT: alanine transaminase

Table III: Demographic, clinical, treatment, characteristics and laboratory findings of patients according to GFR decline rate

	GFR > 5 ml/min/year (n:495 67.2%)	GFR < 5 ml/min/year (n:242 32.8%)	p
Age (years)	62.58 ± 14.80	57.83 ± 15.53	**< 0.001**
< 65	51.5	64	**0.002**
≥ 65	48.5	36	
Gender (%)			0.168
Male	61.2	66.5	
Female	38.8	33.5	
DM (%)	38.4	38	0.936
HT (%)	79.8	73.1	**0.048**
CAD (%)	9.3	10.7	0.597
HF (%)	8.7	6.6	0.387
ACEi/ARB (%)	23	12.8	**0.001**
Statin (%)	29.9	30.6	0.864
Vitamin D (%)	40.4	46.7	0.113
Erythropoietin (%)	7.3	12	**0.038**
GFR (ml/min)	25.05±11.35	20.60±8.12	**< 0.001**
BUN (mg/dl)	46.04±19.02	52.83±17.09	**< 0.001**
Creatinine (mg/dl)	2.97±1.51	3.59±1.32	**< 0.001**
Glucose (mg/dl)	110.54±45.85	111.17±39.84	0.856
Albumin (g/dl)	4.23±0.44	4.16±0.46	**0.031**
LDL (mg/dl)	111.82±32.18	116.13±35.97	0.126
Triglycerides (mg/dl)	148.53±72.92	158.29±89.06	0.151
Potassium (mEq/l)	4.88±0.72	4.97±0.93	0.172
Calcium (mg/dl)	9.27±0.62	9.2 ±0.55	0.191
Phosphorus (mg/dl)	3.99±0.83	4.3±0.78	**< 0.001**
PTH (pg/ml)	159.01±153.6	168.24±108.11	0.355
Uric acid (mg/dl)	6.87±1.44	6.69±1.19	0.111
Hemoglobin (g/dl)	11.88±1.69	11.65±1.48	0.063
HCO3 (mEq/l)	22.78±4.05	22.30±3.08	0.108
HbA1C (%)	6.79±3.74	6.91±5.89	0.803
Proteinuria (g/day)	1.40±2.13	2.07±1.89	**< 0.001**

Note: Values are expressed as $\bar{X}$±SD and percentage (%), DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, HF: heart failure, GFR: glomerular filtration rate, PTH: parathormone, ACEi/ARB: Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker, BUN: blood urea nitrogen, LDL: low-density lipoprotein, Hgb: hemoglobin, HCO3: bicarbonate

The "rapidly progressing" group consisted of 242 patients (161 males, 81 females, mean age 57.83±15.53 years) and the "slowly progressing" group consisted of 495 patients (303 males, 192 females, mean age 62.58±14.80 years). Mean age and age above or below 65 years were significantly associated between the groups ($p<0.05$). There was no statistically significant difference between fasting plasma glucose, LDL, triglyceride, phosphorus, parathormone, uric acid, hemoglobin, bicarbonate, DM, CAD, HF, statin use, vitamin D use and HbA1c levels between the two groups according to GFR progression rate ($p>0.05$). High phosphorus and proteinuria levels, low GFR levels and renin-angiotensin-aldosterone system (RAAS) blocker use were significantly associated with rapid progression, while low albumin, phosphorus, proteinuria levels, high GFR levels and erythropoietin stimulating agent use were significantly associated with slow progression ($p<0.05$).

The correlation analysis of patients' annual GFR decline rate with demographic, clinical and treatment characteristics and laboratory parameters is given in Table IV.

There was no correlation between annual GFR decline rate and gender, diabetes mellitus, coronary artery disease and heart failure, statin, vitamin D, acetyl salicylic acid and allopurinol use, fasting plasma glucose, potassium, calcium, uric acid, ALT, LDL, triglyceride, alkaline phosphatase, hemoglobin, bicarbonate, parathormone, 25OHD3 and HbA1c levels. Significant positive correlations were found between the rate of GFR decline and the presence of hypertension ($r = +0.075$, $P= 0.042$), RAAS blocker use ($r = +0.121$, $P= 0.001$), BUN ($r = +0.171$, $P<0.001$), creatinine ($r = +0.197$, $P<0.001$), phosphorus ($r = +0.179$, $P<0.001$), and proteinuria ($r = +0.150$, $P<0.001$). Significant negative correlations were detected between age ($r = -0.147$, $P < 0.001$), erythropoietin stimulating agent use ($r = -0.078$, $P = 0.034$), GFR ($r = -0.197$, $P < 0.001$) and albumin ($r = -0.080$, $P = 0.031$) levels.

Table IV: Correlation analysis between GFR decline rate and demographic, clinical, treatment characteristics and laboratory findings of the patients included in the study

	GFR decline rate (ml/min/1.73 m²/year)	
	r	p
Age	**-0.147**	**<0.001**
Gender	-0.052	0.161
Diabetes Mellitus	0.004	0.923
Hypertension	**0.075**	**0.042**
Coronary artery disease	-0.023	0.534
Heart failure	0.036	0.330
ACEi/ARB	**0.121**	**0.001**
Statin	-0.007	0.850
Acetyl salicylic acid	0.071	0.055
Allopurinol	-0.021	0.572
Vitamin D	-0.060	0.105
Erythropoietin	**-0.078**	**0.034**
Creatinine (mg/dl)	**0.197**	**<0.001**
BUN (mg/dl)	**0.171**	**<0.001**
GFR (ml/min)	**-0.197**	**<0.001**
Fasting plasma glucose (mg/dl)	0.007	0.856
Albumin (mg/dl)	**-0.080**	**0.031**
ALT (IU/L)	-0.044	0.255
ALP (IU/L)	-0.093	0.057
LDL (mg/dl)	0.061	0.114
Triglycerides (mg/dl)	0.059	0.128
Potassium (mEq/l)	0.055	0.137
Calcium (mg/dl)	-0.046	0.209
Phosphorus (mg/dl)	**0.179**	**<0.001**
PTH (pg/ml)	0.031	0.407
Uric acid (mg/dl)	-0.059	0.111
Hemoglobin (g/dl)	-0.069	0.063
Bicarbonate (mEq/l)	-0.061	0.108
HbA1C (%)	0.013	0.781
25 (OH) D3 (ng/ml)	-0.081	0.157
Proteinuria (g/day)	**0.150**	**<0.001**

DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, HF: heart failure, RAAS: renin angiotensin aldosterone system, PTH: parathormone, ACEi/ARB: Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker, ALT: alanine transaminase, ALP: alkaline phosphatase, Hgb: hemoglobin, 25 (OH) D3: 25 hydroxy cholecalciferol.

Table V shows a multivariate logistic regression study of characteristics that may be related with fast development of GFR. The research revealed a negative relationship between advanced age (≥65) (OR=0.985, p=0.0014) and GFR level (OR=0.972, p=0.010) and GFR decrease rate. Younger patients and those with lower GFR were shown to be at higher risk of CKD progression. There was a statistically significant positive association between rapid progression and RAAS blocker use (OR=1.610, p=0.048) and high phosphorus levels (OR=1.332, p=0.027). RAAS blocker use and high phosphorus levels increased the risk of CKD progression. Diabetes, hypertension, the use of erythropoietin stimulating medications (OR=0.546, p=0.049), albumin, and proteinuria levels were not linked with the rate of CKD development.

Table V: Multivariate logistic regression analysis of factors associated with the rate of decline of GFR

	β	OR	95.0% CI	p
DM	-0.002	0.998	0.680±1.466	0.993
HT	0.186	1.204	0.781±1.856	0.401
ACEi/ARB	0.476	1.610	1.004±2.580	**0.048**
EPO	-0.419	0.658	0.376±1.150	0.142
GFR	-0.028	0.972	0.952±0.993	**0.010**
Albumin	-0.249	0.779	0.490±1.240	0.293
Phosphorus	0.284	1.329	1.033±1.711	**0.027**
Proteinuria	0.016	1.016	0.915±1.128	0.767

OR: odds ratio, ACEi/ARB: Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker, GFR: glomerular filtration rate, DM: diabetes mellitus, HT: hypertension, CI: confidence interval.

Table VI shows the findings of a multivariate cox regression analysis of the variables influencing RRT commencement, death, and RRT/death combination at the conclusion of the follow-up period. As a result, the presence of coronary artery disease, poor GFR, and high proteinuria levels increased the likelihood of RRT advancement, but

Table VI: Multivariate survival analysis of factors associated with RRT, Death (pre-RRT) and RRT/Death endpoints

	RRT			DEATH (pre-RRT)			RRT/DEATH		
	HR	95.0%CI	p	HR	95.0% CI	p	HR	95.0% CI	p
Gender	0.989	0.672-1.455	0.956	1.003	0.534-1.886	0.992	0.984	0.713-1.358	0.924
DM	0.775	0.521-1.152	0.208	1.211	0.613-2.392	0.582	1.009	0.716-1.421	0.960
HT	1.267	0.798-2.010	0.316	0.797	0.345-1.841	0.596	1.189	0.794-1.780	0.401
CAD	0.426	0.245-0.741	0.003	0.522	0.229-1.190	0.122	0.511	0.321-0.814	0.005
CF	0.944	0.390-2.285	0.898	0.135	0.065-0.281	<0.001	0.417	0.251-0.691	0.001
ACEi/ARB	1.155	0.658-2.029	0.616	2.678	1.038-6.913	0.042	1.423	0.876-2.312	0.155
Statin	1.977	1.301-3.006	0.001	1.664	0.777-3.562	0.190	1.797	1.261-2.560	0.001
Vitamin D	1.853	1.276-2.689	0.001	3.286	1.607-6.719	0.001	2.197	1.592-3.034	<0.001
GFR	0.860	0.833-0.889	<0.001	1.021	0.983-1.060	0.919	0.919	0.897-0.940	<0.001
Albumin	1.027	0.635-1.662	0.913	0.218	0.092-0.516	0.001	0.796	0.513-1.236	0.310
Phosphorus	0.934	0.735-1.187	0.579	0.582	0.351-0.967	0.037	0.974	0.784-1.210	0.812
PTH	1.001	0.999-1.002	0.318	0.998	0.994-1.002	0.350	1.000	0.999-1.001	0.807
Hemoglobin	0.886	0.749-1.049	0.161	0.606	0.449-0.818	0.001	0.764	0.675-0.866	<0.001
Proteinuria	1.168	1.095-1.246	<0.001	1.101	0.885-1.370	0.389	1.142	1.072-1.216	<0.001

HR: hazard ratio, RRT: renal replacement therapy, DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, HF: heart failure, GFR: glomerular filtration rate, PTH: parathormone, ACEi/ARB: Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker, Hgb: hemoglobin

statin and vitamin D usage reduced RRT progression. Heart failure, anemia, and hyperphosphatemia raised the risk of death, but RAAS blockers, vitamin D, and high blood albumin levels lowered the risk of death. The presence of coronary artery disease and heart failure, anemia, low GFR, and high proteinuria all raised the chance of progression to the combined endpoint of RRT/death, but statin and vitamin D therapy, as well as high hemoglobin levels, significantly decreased this risk.

DISCUSSION

CKD is characterized by the increasing loss of functioning nephrons. The increasing incidence of CKD causes significant workforce loss, economic, social, and psychological problems. The development of CKD to ESRD is a worldwide public health concern; hence, avoiding CKD or delaying progression to ESRD would not only enhance patients' quality of life and length of life but will also significantly lower the cost burden of this illness on health systems. Much prior research has explored the effects of age and gender on CKD advancement, and it has been demonstrated that advanced age and male gender accelerate CKD progression (9, 10). Eriksen et al., found that advanced age and male gender enhanced the risk of progression to ESRD and death in a large cohort of 58000 individuals with stage 3-4 CKD (9). In a study conducted by Xu et al., on 15370 individuals including both healthy and CKD populations, it was shown that old age and older male gender increased the risk of CKD progression (10). In our study, the progression rate was greater in younger individuals with a mean age of 61 years than in older patients. Furthermore, the mortality risk was considerably greater in patients aged 65 and older, but no influence of age or gender on the length of RRT commencement could be observed.

Hypertension is a risk factor for the development of CKD and progression to ESRD on its own (11). In patients with chronic kidney disease, systemic hypertension causes progressive nephron loss, leading to intraglomerular hypertension in the remaining nephrons, increased net filtration pressure and increased proteinuria (12). In our study, there was no significant difference in the prevalence of hypertension between the groups based on GFR stage, however there was a significant difference between the two groups based on GFR decline rate. In univariate analysis, the pres-

ence of hypertension was related with rapid advancement of CKD, but multivariate analysis revealed no influence on the pace of progression. Furthermore, hypertension had no influence on the endpoints of renal replacement therapy initiation and mortality.
Proteinuria has been established in previous research to be a substantial independent risk factor for progression to ESRD and all-cause death (13, 14). Proteinuria is a major risk factor for renal function degradation and progression to CKD in both healthy and CKD patients (15-20). Proteinuria was discovered to be definitively linked with renal disease prognosis in both diabetic and non-diabetic individuals with CKD (21). In a meta-analysis published by Astor et al., including data from 21688 patients with chronic kidney disease, it was shown that low GFR and albuminuria/proteinuria significantly increased progression to ESRD and mortality (22). Again, a 50% reduction in proteinuria was demonstrated to significantly lower the risk of progression to ESRD and death in a meta-analysis reported by Inker et al. that included data from 9008 individuals (23). This study, like others, found that reducing blood pressure in diabetic nephropathy patients with overt proteinuria improves kidney disease outcomes.

Proteinuria is the most important modifiable risk factor in chronic kidney disease, and its reduction should be the primary target of treatment; ACE inhibitors and ARB group medicines used for this purpose have an antiproteinuric effect. Drugs that block the RAAS suppress local angiotensin II formation or action, resulting in decreased intraglomerular pressure, proteinuria and local release of chemokines and cytokines. Several randomized trials in diabetic and nondiabetic patients with CKD have shown a more effective antiproteinuric effect of RAAS blockers compared with placebo and/or other antihypertensives. This significantly reduces long-term progression of CKD (24, 25). In our study, it was observed that the amount of proteinuria increased as the GFR stage increased. Not only will proteinuria increase as chronic kidney disease progresses, but proteinuria itself is also likely to progress the disease. Proteinuria was greater in the fast progressing group than in the slowly moving group, based on the rate of GFR reduction. Proteinuria was found to be linked with CKD development in univariate analysis, but not with the rate of GFR reduction in logistic regression analysis. Furthermore, a positive link was discovered between proteinuria levels and RRT and RRT/death endpoints; as the amount of proteinuria grew, so did the likelihood of advancement to RRT and RRT/death endpoints, and survival reduced. The Diabetes Management and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) both found that glycemic control protects microalbuminuria in diabetic individuals (26, 27). The Kidney/Dialysis Outcomes Quality Initiative (K/DOQI) guidelines emphasize the need for tight glycemic control to slow the progression of microvascular complications of diabetes, especially diabetic nephropathy, with a target HbA1c below 7%. In our study, there was no significant difference in HbA1c levels between the two groups based on the rate of GFR decrease, and there was no influence of HbA1c level on CKD advancement.

Lipid metabolism disorders are an independent risk factor not only for cardiovascular diseases but also for the onset and progression of CKD (27). A meta-analysis published by Sandhu et al., showed that statin therapy mildly reduced albuminuria/proteinuria and loss of renal function, especially in patients with cardiovascular disease (28). In contrast, two separate meta-analyses published by Nikolic et al., and Su et al., showed that statins may have significant renoprotective effects in patients with chronic kidney disease, but that this was related to the duration of treatment; they also did not change the progression to renal failure in patients with CKD who did not receive replacement therapy, but may modestly reduce the rate of proteinuria and GFR decline (29, 30). In our study, no significant difference was found between the two groups in terms of statin use, LDL and triglyceride levels according to GFR progression rate. In this study, serum lipid levels and lipid-lowering treatment had no effect on the rate of decrease in GFR. However, there was a negative association between statin use and RRT and progression to RRT/death endpoints; the risk of RRT initiation and progression to RRT/death endpoints was lower in statin users compared to non-users.

Anemia is considered an indicator of progression of CKD and progression to ESRD (31). Anemia is a predictive indicator for tissue hypoxia leading to renal tissue damage. Tubular cell hypoxia in people with reduced nephron number is due to increased oxygen consumption by tubule cells in the remaining nephrons and reduced interstitial capillary count (32). In rats with acute ischemic renal injury, renal dysfunction and morphological damage were reduced with the use of erythropoietin; this is most likely due to the reduction of apoptotic cell death (33).
In our study, a decrease in hemoglobin levels and an increase in erythropoietin use were observed as the stage of CKD increased and the difference between the groups was significant. We also found that anemia increased the risk of death and progression to RRT/death endpoints.

In CKD patients, hyperphosphatemia and hyper-hypoparathyroidism lead to vascular and visceral calcification and increase the risk of cardiovascular and all-cause mortality (34). High calcium-phosphorus product adversely affects intrarenal vasculopathy, stimulates tubulointerstitial inflammation and fibrosis and leads to calcification, ultimately shortening renal and patient survival. Oral paricalcitol has antiproteinuric effect in patients with CKD (35). Vitamin D has anti-inflammatory, antiproliferative and immune modulatory effects in general. Active vitamin D is a negative endocrine regulator of RAAS (36). In our study, as expected, a decrease in calcium levels and a significant increase in phosphorus and PTH levels were observed as the GFR stage increased between the groups.

Again, a significant difference was found in phosphorus levels between the two groups according to GFR progression rate, but calcium and PTH levels were similar between the two groups. Univariate and logistic regression analysis showed a significant association between phosphorus level and rapid progression and hyperphosphatemia increased the risk of rapid progression. In addition, hyperphosphatemia increased the risk of progression to the endpoint of death and decreased survival, whereas PTH and calcium levels had no effect on RRT, death and progression to RRT/death endpoints. In our study, vitamin D use was shown to improve survival and reduce the risk of RRT. Symptomatic or asymptomatic hyperuricemia is associated with CKD progression. Previous studies have shown that uric acid-lowering therapy slows the rate of disease progression in diabetic and non-diabetic patients with CKD (37-39). In our study, no effect of serum uric acid levels on the rate of CKD progression, initiation of RRT and progression to the endpoints of death could be demonstrated. Our research has a few limitations. Body mass index, dietary features, oxidative stress, inflammation, and endothelial dysfunction measures, and whether these variables and/or race and genetic traits contribute to disease development were unclear.

CONCLUSION

According to our findings, the usage of RAAS blockers and hyperphosphatemia accelerated the advancement of renal disease. The presence of coronary artery disease and high proteinuria levels elevated the likelihood of RRT beginning in our research, but statin and vitamin D usage lowered this risk. Furthermore, the presence of heart failure, hyperphosphatemia, and anemia raised the risk of death, but the use of RAAS blockers, vitamin D, and high albumin levels reduced the risk of mortality. To summarize, CKD is a progressive illness with a high morbidity and fatality rate. Recognizing and addressing the causes that promote this disease's development will increase patient survival.

Ethics Committee Approval:
The study was approved, and the requirement for informed consent was waived by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (Decision number:8 Date:06th January 2016). The present study was conducted in line with the Declaration of Helsinki.

Informed Consent:
Informed consent was not obtained as it was a retrospective clinical study.

Author Contributions:
Concept – S.B.,G.S.; Design - S.B.,G.S.; Supervision - S.B.,G.S.,M.D.; Resources - S.B.,G.S.,M.D.; Materials- S.B.,G.S.,M.D.; Data Collection and/or Processing - S.B.,G.S.,M.D.; Analysis and/ or Interpretation - S.B.,G.S.,M.D.; Literature Search - S.B.,G.S.,M.D.; Writing Manuscript - S.B.,G.S.,M.D.; Critical Review - S.B.,G.S.,M.D.

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