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Original Article

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Determinants of Mortality Among Elderly Subjects with Chronic Kidney Disease

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ABSTRACT

Objective: Studies on predictors of mortality among elderly chronic kidney disease (CKD) patients have conflicting results. We aimed to assess the factors related to mortality in CKD versus non-CKD elderly subjects.
Methods: Medical records of consecutive elderly subjects presented to geriatrics outpatient clinics were retrospectively searched. Logistic regression models were set in order to determine independent predictors of mortality.
Results: The median age was 73 (67-80) years, and 837 (67.9%) were female. CKD constituted 21.9% of the cohort. During the follow-up of 3 to 4 years, 7.2% of the patients died. In the CKD cohort, older age (per year, OR 1.12, 95% CI 1.01-1.25, *P* = .040) and serum uric acid levels (per 1 mg/dL increase, OR 1.74, 95% CI 1.12-2.69, *P* = .013) were associated with a higher risk of mortality while serum albumin (per 1 g/dL increase, OR 0.08, 95% CI 0.01-0.52, *P* = .008) and vitamin D levels (per 1 ng/mL increase, OR 0.77, 95% CI 0.62-0.96, *P* = .019) were associated with a lower risk of mortality in the multivariate regression model.
Conclusion: Older age, lower serum albumin and vitamin D levels, and higher serum uric acid levels are independent predictors of mortality in outpatient elderly subjects with CKD.
Keywords: Aged, mortality, chronic renal insufficiency

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INTRODUCTION

Chronic kidney disease (CKD) is a global health problem affecting a considerable percentage of the adult population all over the world,[1] and represents a risk factor for mortality.[2] As the severity of kidney disease increases, traditional and non-traditional risk factors emerge, and CKD becomes a more unique state significantly associated with increased risk of mortality caused by cardiovascular disorders and many other etiologies.[3-4]

There may be several explanations for this increased risk of mortality during the course of CKD. In the study by Landray et al.[5] authors evaluated outcomes of predialysis CKD patients. The authors found that age and smoking were independent risk factors for death along with serum cardiac biomarkers. In another study,[6] Tsur et al.[6] investigated whether clinical and biochemical factors at the predialysis stage had an impact on patient mortality after the commencement of dialysis in diabetic CKD patients. Lower body mass index, pulse pressure, and cardiovascular comorbidity at the predialysis stage independently predicted mortality after the initiation of dialysis. In another study,[7] in addition to age, low body mass index, history of cardiovascular disease or cancer, and several baseline laboratory parameters including hemoglobin, ferritin, C-reactive protein, serum albumin, and creatinine were independent predictors of death.

Patients with CKD frequently represent a rather old population, however, it is unknown whether predictors of mortality among the geriatric age group with CKD differ

or not. With this study, we aimed to investigate the effects of kidney function on patient survival, assess independent predictors of mortality, and examine differences between predictors of death in CKD and non-CKD groups of elderly people.

METHODS

Consecutive elderly subjects (≥65 years) presented to the geriatric outpatient clinics between August 2016 and October 2017 were included. Medical records were obtained from patient files. Patients were followed for 3-4 years. Records included age, sex, comorbidities, Charlson comorbidity index, duration of education (by years), number of drugs, body mass index, systolic and diastolic blood pressure, hemoglobin, serum creatinine, serum albumin, blood electrolyte levels, HbA1-c, lipid profile, vitamin D, vitamin B12, folic acid, and serum uric acid.

Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2 and graded according to consensus guidelines.[8] GFR was estimated according to the chronic kidney disease epidemiology collaboration (CKD-EPI) formula.[9]

This study was approved by the Ethics Committee of Bezmialem Vakıf University (01.07.2020/06-04).

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). A *P*-value of < .05 was considered statistically significant. The distribution of data was assessed using the Kolmogorov–Smirnov test. Continuous variables were expressed as median with the interquartile range (25-75%) if non-normally distributed and as mean ± standard deviation, vice versa. Categoric variables were expressed as proportions. Chi-squared tests were used for comparing qualitative measures between CKD and non-CKD cohorts. Comparisons of continuous variables between these groups were performed using the Mann-Whitney *U*-test. Logistic regression models were used in order to determine independent predictors of mortality in the entire cohort, patients with CKD, and the non-CKD cohort. In addition to age and sex, variables that reached a *P*-value of < .05 in univariate analysis were included in multivariate models. Backward elimination method was used in multivariate analysis.

Main Points

- The risk of mortality in elderly people increases with each decline in eGFR. In a CKD cohort, older age and higher serum uric acid levels are independently associated with a higher risk of mortality while higher serum albumin and vitamin D levels are associated with a lower risk of mortality. On the other hand, in the non-CKD cohort, older age and the presence of congestive heart failure are independently associated with mortality while a higher serum albumin level is associated with a lower risk of death.

RESULTS

One thousand forty patients were included in the study. The mean age was 74 ± 8 years and 837 (67.9%) were female. Chronic kidney disease was evident in 265 (21.9%) of patients, while the CKD status of 11 (0.9%) patients was not available due to lack of serum creatinine measurement.

Patients with CKD were older (*P* < .001), had a higher median Charlson comorbidity index (*P* < .001), and were using more drugs (*P* < .001). Hypertension was more frequent in the CKD cohort (*P* = .003), comprising 71.7% of the subjects. Mean body mass index was higher in the non-CKD cohort (*P* = .047). In addition to significant differences for serum creatinine (mean 1.37 mg/dL vs. 0.73 mg/dL), eGFR (mean 48 mL/min/1.73 m^2 vs. 85 mL/min/1.73 m^2), hemoglobin (mean 12.9 g/dL vs. 14.0 g/dL), serum potassium (median 4.6 mEq/L vs 4.4 mEq/L), serum uric acid (mean 7.0 mg/dL vs. 5.3 mg/dL), and serum folic acid (median 7.3 ng/mL vs. 8.8 ng/mL), and serum vitamin B12 level (median 168 pg/mL vs 241 pg/mL) were also significantly different among CKD and non-CKD cohorts (*P* < .001 for all comparisons, Table 1).

During the follow-up, 89 (7.2%) of the patients died, and survival data of 193 patients were unavailable. Risk of mortality was decreased with each increase in eGFR (per 1 mL/min/1.73 m^2 increase, OR 0.98, 95% CI 0.97-0.99, *P* < .001) and with each decline in CKD stage (per grade, OR 1.68, 95% CI 1.30-2.18, *P* < .001). Odds ratio of mortality in patients who had an eGFR of <90, <60, <45, and <30 mL/min/1.73 m^2 were 2.06, 2.49, 3.43, and 4.84, respectively (Table 2).

Age, years of education, presence of heart failure, body mass index, hemoglobin, serum albumin, eGFR, serum calcium, serum magnesium, serum uric acid, vitamin D, and LDL-cholesterol levels were significant parameters associated with death in univariate analysis. After including sex and all these significant parameters in the multivariate regression model, older age (per year, OR 1.07, 95% CI 1.02-1.12, *P* = .007) and higher serum uric acid (per 1 mg/dL, OR 1.30, 95% CI 1.06-1.60, *P* = .013) were independently associated with mortality, while a higher serum albumin (per 1 g/dL increase, OR 0.31, 95% CI 0.11-0.87, *P* = .026), vitamin D (OR 0.95, 95% CI 0.91-1.00, *P* = .055), and serum LDL-cholesterol (OR 0.99, 95% CI 0.98-1.00, *P* < .001) were significantly associated with a lower risk of death (Table 3). In the CKD cohort, older age (OR 1.12, 95% CI 1.01-1.25, *P* = .040) and higher serum uric acid levels (OR 1.74, 95% CI 1.12-2.69, *P* = .013) were independently associated with a higher risk of mortality while higher serum albumin (OR 0.08, 95% CI 0.01-0.52, *P* = .008), and vitamin D levels (OR 0.77, 95% CI 0.62-0.96, *P* = .019) were associated with a lower risk of mortality in the multivariate regression model. In the non-CKD cohort, older age (OR 1.08, 95% CI 1.04-1.13, *P* < .001) and the presence of congestive heart failure (OR 3.03, 95% CI 1.12-8.20, *P* = .029) were independently associated with mortality while a higher serum albumin level (OR 0.20, 95% CI 0.07-0.56,

Table 1. General Characteristic of All Patients, and Chronic Kidney Disease (CKD) and Non-CKD Cohorts

Variables[a]	All Patients (*n* = 1233)[b]	CKD (*n* = 265)	Non-CKD (*n* = 957)	*P*
Age, years	74 ± 8	78 ± 7	73 ± 8	<.001
Female	67.9%	63.4%	69.1%	.080
Years of education	3 (0-5)	3 (0-5)	3 (0-5)	.238
Diabetes mellitus	34.8%	37.7%	34.1%	.157
Hypertension	65.7%	71.7%	63.9%	.003
Charlson comorbidity index	1 (0-1)	1 (0-2)	0 (0-1)	<.001
Number of drugs	4 (2-6)	5 (3-8)	4 (2-6)	<.001
Diuretics	45.7%	57.8%	43.4%	<.001
Body mass index	31.5 ± 5.8	40.8 ± 6.3	31.7 ± 5.7	.047
SBP, mmHg	145 ± 27	143 ± 29	145 ± 26	.672
DBP, mmHg	79 ± 15	79 ± 16	80 ± 14	.180
Serum creatinine, mg/dL	0.87 ± 0.46	1.37 ± 0.65	0.73 ± 0.26	<.001
eGFR, mL/min/1.73 m^2	77 ± 21	48 ± 20	85 ± 13	<.001
Hemoglobin, g/dL	13.8 ± 3.9	12.9 ± 1.8	14.0 ± 4.2	<.001
Serum albumin, g/dL	4.2 ± 1.3	4.1 ± 0.4	4.3 ± 1.5	<.001
Serum sodium, mmol/L	140 (137-141)	140 (137-141)	140 (137-142)	.587
Serum potassium, mEq/L	4.4 (4.2-4.7)	4.6 (4.3-5.0)	4.4 (4.2-4.6)	<.001
Serum calcium, mg/dL	9.5 (9.2-9.8)	9.4 (9.1-9.8)	9.5 (9.2-9.8)	.163
Serum phosphorus, mg/dL	3.3 (3.0-3.7)	3.3 (3.0-3.7)	3.3 (2.9-3.6)	.138
Serum magnesium, mg/dL	2.0 (1.8-2.2)	2.0 (1.8-2.2)	2.0 (1.8-2.1)	.572
Vitamin D, ng/mL	12.4 (9.0-22.2)	10.5 (9.0-22.7)	12.6 (9.0-22.1)	.222
Serum uric acid, mg/dL	5.7 ± 1.6	7.0 ± 1.7	5.3 ± 1.4	<.001
LDL-cholesterol, mg/dL	126 ± 40	121 ± 40	127 ± 39	.041
HbA1-c, %	6.2 (5.7-7.3)	6.3 (5.8-7.5)	6.2 (5.7-7.2)	.395
Folic acid, ng/mL	8.5 (6.4-11.1)	7.3 (5.5-9.8)	8.8 (6.7-11.3)	<.001
Vitamin B12, pg/mL	229 (163-338)	168 (181-144)	241 (155-311)	<.001

[a]Continuous variables are expressed as median with interquartile range (25%-75%), or mean±SD, as appropriate. [b]Eleven patients did not have a serum creatinine measurement.
DBP, diastolic blood pressure, Egfr, estimated glomerular filtration rate, SBP, systolic blood pressure

Table 2. Effects of Glomerular Filtration Rate (eGFR) Cutt-Off on Patient Survival

Parameter	Odds Ratio
eGFR, per 1 mL/min/1.73 m^2 increase	OR 0.98, 95% CI 0.97-0.99, *P* < .001
eGFR < 90 mL/min/1.73 m^2	OR 2.06 95% CI 1.22-3.48, *P* = .007
eGFR < 60 mL/min/1.73 m^2	OR 2.49, 95% CI 1.53-4.03, *P* < .001
eGFR < 45 mL/min/1.73 m^2	OR 3.43, 95% CI 1.85-6.39, *P* < .001
eGFR < 30 mL/min/1.73 m^2	OR 4.84, 95% CI 1.81-12.92, *P* = .002
CKD, decline per each stage	OR 1.68, 95% CI 1.30-2.18, *P* < .001

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); OR, odds ratio

P = .002) was associated with a lower risk of death in the multivariate regression model.

CRP was available in a subset of patients (719 of 1233). When we classified patients according to serum uric acid levels as hyperuricemia (>7 mg/dL) versus normouricemia (4-7 mg/dL), the former group had significantly higher CRP level (mean 8.4 mg/L vs 6.6 mg/L, *P* = .001). CRP levels were significantly associated with an increased risk of mortality in univariate analysis (per 1 mg/L, OR 1.03), but not in multivariate models for the overall, CKD and non-CKD cohorts. We have not included this data in Table 3 due to the high number of cases with missing CRP. Similar to CRP levels, the Charlson comorbidity index was also significantly associated with an increased risk of mortality in

Table 3. Predictors of Mortality in Overall, Chronic Kidney Disease (CKD), and Non-CKD Cohorts According to Logistic Regression Models

	Overall		CKD		Non-CKD	
Parameters	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Age per 1 year increase	OR 1.12, 95% CI 1.09-1.15, *P* < .001	**OR 1.07, 95% CI 1.02-1.12, *P* = .007**	OR 1.09, 95% CI 1.02-1.15, *P* = .007	**OR 1.12, 95% CI 1.01-1.25, *P* = .040**	OR 1.12, 95% CI 1.08-1.16, *P* < .001	**OR 1.08, 95% CI 1.04-1.13, *P* < .001**
Male	OR 1.02, 95% CI 0.62-1.68, *P* = .935	-	OR 1.18, 95% CI 0.46-3.00, *P* = .734	-	OR 0.99, 95% CI 0.54-1.82, *P* = .972	-
Years of education per year	OR 0.90, 95% CI 0.83-0.98, *P* = .015	-	-	-	-	-
Congestive heart failure	OR 2.94, 95% CI 1.42-6.10, *P* = .004	-	-	-	OR 2.88, 95% CI 1.15-7.21, *P* = .024	**OR 3.03, 95% CI 1.12-8.20, *P* = .029**
Body mass index per 1 kg/m^2 increase	OR 0.94, 95% CI 0.90-0.99, *P* = .021	-	OR 0.91, 95% CI 0.84-0.99, *P* = .036	-	-	-
Hemoglobin per 1 g/dL increase	OR 0.83, 95% CI 0.73-0.95, *P* = .005	-	OR 0.75, 95% CI 0.60-0.94, *P* = .012	-	-	-
Serum albumin per 1 g/dL increase	OR 0.09, 95% CI 0.05-0.17, *P* < .001	**OR 0.31, 95% CI 0.11-0.87, *P* = .026**	OR 0.08, 95% CI 0.03-0.27, *P* < .001	**OR 0.08, 95% CI 0.01-0.52, *P* = .008**	OR 0.10, 95% CI 0.04-0.22, *P* < .001	**OR 0.20, 95% CI 0.07-0.56, *P* = .002**
eGFR*	OR 0.98, 95% CI 0.97-0.99, *P* < .001	-	-	-	OR 0.97, 95% CI 0.95-0.99, *P* = .005	-
eGFR < 60 mL/min/1.73 m^{2*}	OR 2.49, 95% CI 1.53-4.03, *P* < .001	-	n/a	-	n/a	-
Serum calcium per 1 mg/dL increase	OR 0.42, 95% CI 0.28-0.63, *P* < .001	-	OR 0.36, 95% CI 0.18-0.72, *P* = .004	-	OR 0.50, 95% CI 0.30-0.83, *P* = .008	-
Serum magnesium per 1 mg/dL increase	OR 0.40, 95% CI 0.17-0.94, *P* = .035	-	-	-	OR 0.24, 95% CI 0.08-0.74, *P* = .013	-
Serum uric acid per 1 mg/dL increase	OR 1.32, 95% CI 1.17-1.49, *P* < .001	**OR 1.30, 95% CI 1.06-1.60, *P* = .013**	OR 1.29, 95% CI 1.03-1.62, *P* = .025	**OR 1.74, 95% CI 1.12-2.69, *P* = .013**	-	-
Vitamin D per 1 ng/mL increase	OR 0.96, 95% CI 0.93-0.99, *P* = .003	**OR 0.95, 95% CI, 0.91-1.00, *P* = .055**	OR 0.94, 95% CI 0.88-1.00, *P* = .057	**OR 0.77, 95% CI 0.62-0.96, *P* = .019**	OR 0.96, 95% CI 0.93-1.00, *P* = .029	-
LDL cholesterol per 1 mg/dL increase	OR 0.99, 95% CI 0.98-0.99, *P* < .001	**OR 0.99, 95% CI 0.98-1.00, *P* = .019**	OR 0.99, 95% CI 0.97-1.00, *P* = .008	-	OR 0.99, 95% CI 0.98-0.99, *P* < .001	-

*These variables were included in different models, separately. Empty blanks denote non-significant associations.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate, n/a: not applicable, OR, odds ratio

univariate analysis (per 1 point, OR 1.03), but not in multivariate models. Missing cases were also high in number for this index, so this is not mentioned in Table 3 either.

DISCUSSION

We have demonstrated that along with older age and lower serum albumin levels which were independently associated with mortality in both CKD and non-CKD cohorts, a higher serum uric acid and a lower serum 25-OH vitamin D levels were independent predictors of mortality among elderly subjects with CKD.

Inverse effects of older age and hypoalbuminemia on mortality in CKD patients or maintenance dialysis have been described by others.[6,7] Possible role of serum uric acid with mortality in patients with CKD is intriguing and has been described more than a decade ago as associations between uric acid with metabolic disorders and inflammation.[10] Further associations

of serum uric acid with increased risk of mortality among CKD patients have been reported by many studies and meta-analyses.[11-16] In our study, serum uric acid level was an independent predictor of mortality in CKD, but not in the non-CKD cohort. The reason for this may be the absence of other risk factors for organ damage in the non-CKD cohort. In a paper by Navaneethan et al.,[17] authors concluded that hyperuricemia was associated with mortality in a non-CKD population. It was speculated that the presence of CKD attenuated the association between serum uric acid and mortality. Though some studies demonstrated the relationship of serum uric acid with progression of CKD, a randomized controlled trial[18] which included subjects with a high risk of progression (those with albuminuria and rapid GFR decline) could not demonstrate a benefit of urate-lowering with allopurinol on the progression of kidney disease. Another recent randomized controlled trial[19] included patients with type 1 diabetes mellitus who received allopurinol versus placebo. The results were similarly negative. Allopurinol did not reduce the risk of kidney disease progression in any of these recent studies despite the expected decrease in serum uric acid levels in both. A prospective controlled study from China[20] reported a better efficacy of febuxostat over allopurinol, and reduction in serum uric acid levels was significantly associated with a slower progression of kidney disease.

The effect of 25-OH vitamin D levels on outcomes of CKD patients is unclear. The most recent CKD-mineral bone disorder KDIGO guideline stated that vitamin D levels might be measured and deficiency or insufficiency may be corrected using a similar treatment strategy recommended for the general population, with a quality of evidence of 2C.[21] Chonchol and Scragg examined associations between kidney function with serum levels of calcidiol and components of the metabolic syndrome, and it was observed that these patients did not have vitamin D deficiency in the absence of severe renal impairment (CKD stage 4 or worse) (22). Similar to assumptions that have been made for many other associations between vitamin D levels with cancers and other many disorders, vitamin D may rather represent indirect evidence for the general well-being and nutrition status of a person.

The association of CKD with mortality was also quite significant in the univariate analysis in the entire cohort, although the significance was lost in multivariate regression models. There has been a debate about considering elderly subjects with an eGFR of < 60 mL/min/1.73 m^2 as CKD patients.[23] According to meta-analyses, mortality rate significantly increases if eGFR is less than 75 mL/min per 1.73 m^2 among young people, while a similar increase in mortality among elderly people was observed when eGFR is less than 45 mL/min per 1.73 m^2.[23] In addition, it was found that GFR declines with the normal aging process without any signs of hyperfiltration or kidney damage.[23] When we defined CKD as an eGFR of < 45 mL/min per 1.73 m^2, results were similarly significant in univariate, but not in multivariate analysis. Reasons for this may be the relatively low number of patients with higher stages of CKD. In addition, urinary albumin excretion was not available which would help to classify subjects as CKD in a more reliable manner. Briefly, the reason for non-significant results in multivariate regression models might be the possible misclassification of patients as CKD and non-CKD.

Our study has several limitations. In addition to its retrospective design, the classification of patients as CKD and non-CKD may be inaccurate in some. Laboratory measurements that were performed in one visit were taken into account, and urinary protein excretion values were not available. These would have strengthened the reliability of the classification of patients into groups. Moreover, despite the follow-up of 3 to 4 years, the actual death dates of the subjects were not known. So, we have performed logistic regression models and defined several parameters which were associated significantly with the risk of death during this follow-up period. It would be more accurate to perform cox-regression analysis in order to calculate the hazard ratio of each variable for association with mortality. We were not able to access drug exposures in all cases. Drugs that have an impact on serum uric acid levels may have changed some results, making it hard to reach a solid conclusion. . . Results of our paper are not novel and require careful interpretations due to these limitations.

In conclusion, older age, lower serum albumin, lower 25-OH vitamin D and higher serum uric acid levels are independent predictors of mortality in elderly subjects with CKD.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Committee of Bezmialem Vakıf University (01.07.2020/06-04).

Informed Consent: Written informed consent was obtained from all participants who participated in this study or from a legal guardian.

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