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Peripheral Neuropathy Associated with Higher Mortality in Population with Chronic Kidney Disease: National Health and Nutrition Examination Surveys

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Keywords
Chronic kidney disease · Peripheral neuropathy · Mortality · National Health and Nutrition Examination Survey

Abstract
Introduction: Peripheral neuropathy (PN), one of the commonest neurological complications of chronic kidney disease (CKD), was associated with physical limitation. Studies showed that a decrease in physical capability in patients with CKD is related with an increased risk of mortality. The objective of our research was to directly explore the relationship between PN and risk of mortality in patients with CKD. ***Method:*** 1,836 participants with CKD and 6,036 participants without CKD, which were classified by PN based on monofilament examination in National Health and Nutrition Examination Survey (NHANES), were collected from the 1999 to 2004 National Health and Nutrition Examination Surveys. Multivariable Cox proportional hazard models were conducted to assess the relationships of PN and deaths in patients with CKD and non-CKD. ***Results:*** During 14 years of a median follow-up from 1999 to 2015 and 2004 to 2015, 1,072 (58.4%) and 1,389 (23.0%) deaths were recorded in participants with CKD and without CKD, respectively. PN was related with increased all-cause mortality even after adjusting possible confounding factors in population with CKD (hazard ratio [HR] 1.34, 95% confidence interval [CI] 1.17–1.53) and without CKD (HR 1.27, 95% CI 1.12–1.43). And the adjusted HRs (95% CI) for cardiovascular mortality of the people with CKD and without CKD who suffered from PN were 1.42 (1.07, 1.90) and 1.23 (0.91, 1.67), respectively, versus those without PN. ***Conclusion:*** PN was related with a higher risk of all-cause and cardiovascular death in people with CKD, which clinically suggests that the adverse prognostic impact of PN in the CKD population deserves attention and is an important target for intervention.

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Introduction

Peripheral neuropathy (PN) is one of the most common neurological complication of CKD and is also particularly prevalent in adults with diabetes. One of the features of large-fiber peripheral polyneuropathy, which occurs through pain, sensory loss, and muscle weakness, especially expressed in foot complications,

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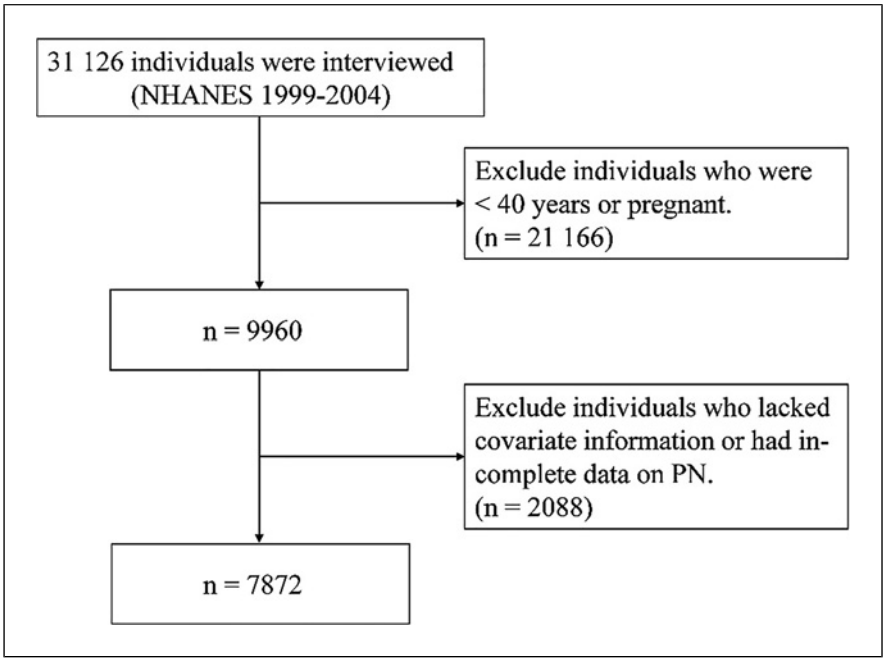

Fig. 1. Flow diagram of the selection of eligible participants, National Health and Nutrition Examination Survey 1999–2004.

is decreased tactile sensation [1]. Extent of renal impaired function was found to play a key role in the progression of neuropathy, with the glomerular filtration rate falls below 12 mL/min reported concomitant clinically significant neuropathy [2]. 60–90% of dialysis patients of whom have long been considered to have advanced CKD suffer from PN [3, 4]. Recently, the presence of PN in early CKD has been demonstrated in both whole population and CKD population studies [5–8].

Physical limitations like poor exercise tolerance [9], reduced functional capacity, muscle atrophy [10], falls [11], and fractures [12] are often seen in patients with renal insufficiency, which is usually attributed to neurological complications occurring in most patients with chronic kidney disease (CKD) [4]. One study has reported an association between PN and walking speed with quality of life in patients with CKD [13]. There is also research showing that a decrease in walking speed in patients with stage 2–4 CKD was related with a growth of risk of death [14]. Therefore, there may be a relationship between PN and death risk in patients with CKD, which has not been investigated previously. The objective of our research was to directly explore the relationship of PN and death risk in participants with CKD and to discuss the contribution of diabetes in this context.

Method

Study Population

The data we employed was available from National Health and Nutrition Examination Survey (NHANES) 1999–2004, comprising nationally representative samples of the population of non-institutionalized US civilians, which executed by the National Center for Health Statistics (NCHS) of the Center for Disease Control (CDC). Interview and a physical examination were executed by standardized staff to the participants chosen by NHANES in their home and in a mobile examination center (MEC), respectively.

The NHANES survey cycles from 1999 to 2004 included 31,126 US adults. Participants aged 40 years old or over who attended the lower extremity disease examination (the 40 years of age and older group was considered to be at high risk for lower extremity disorders and was asked to participate in the PN Section of the Lower Extremity Disease examination) and had complete data on PN, mortality status, and follow-up time (n = 8,717) were included in our research [15]. We excluded participants who were pregnant (n = 21,166). Participants who were missing covariates of interest (n = 845) were also excluded. In results, we obtained a final sample size of 7,872 persons (Fig. 1), which were stratified by CKD status based on the definition as estimated glomerular filtration rate (eGFR) of 15–59 mL/min/1.73 m^2 or urinary albumin-to-creatinine ratio (ACR) at least 30 mg/g (No. of CKD = 1,836, No. of non-CKD = 6,036).

It is publicly available for the information from NHANES, and we employed for a secondary analysis that organizational review board ratification is unwarranted. And all examinations were conducted after signing informed consent from the qualified candidates.

Measurement of PN

Monofilament examination detecting a single point of gentle tap force was conducted by highly trained medical staff to assess PN. The sole of every subject in NHANES on 3 neighboring margins between the phalanx and the 1st phalanx head, the 5th metatarsal head, and hallux was delivered approximately 10 g pressure using a 5.07 Semmes-Weinstein nylon monofilament by trained technicians [16]. Three neighboring margins between the phalanx and the first phalanx head, the fifth metatarsal head, and the meniscus.

An absence of sensation was defined by two times of incorrect or indeterminable identification or one incorrect versus one indeterminable identification where the force was exerted. And the highest times of 3 examinations were performed for a site if former 2 times were not similar. Then participants with at the minimum one insensate point on either foot were considered with PN.

Assessment of Kidney Function

Urine albumin was measured by a solid-phase fluorescence immunoassay. Serum creatinine and urine creatinine were measured by the modified Jaffé kinetic method. The values of the serum were used to calculate eGFR by CKD Epidemiology Collaboration (CKD-EPI) [17], which from 1999 to 2000 had been calibrated by Cleveland Clinic laboratory standards [18]. The status of CKD was defined by the value of eGFR and urine albumin.

Covariates

We collected demographic data from the interview information of the NHANES, which included age, gender, ethnicity classified as Mexican American/non-Hispanic black/non-Hispanic white/other, married status classified as married/unmarried, level of education classified as less than high school/high school graduates or equivalent/some college or above, level of family poverty income ratio classified as ≤1/>1–<4/≥4, alcohol drinking status classified as nondrinkers, moderate drinkers, binge drinkers, and heavy drinkers, and the status of cigarette smoking defined as current smoking, former smoking, and never smoking. The value of body mass index (BMI) was calculated by weight (kg) divided by square of height (m^2). The status of leisure-time physical activity was regarded as whether more than 10 min of vigorous/moderate recreational activity per week. Details of data collection and definition have been stated elsewhere [19].

Data on serum potassium ion concentrations were obtained from the MEC. Hyperlipidemia was identified by the ratio of total cholesterol and high-density lipoprotein at least 5.9%. Participants in the status of currently administering antihypertensive medication or with mean systolic blood pressure more than 140 mm Hg or diastolic blood pressure more than 90 mm Hg were defined as falling ill with hypertension. Participants with fasting plasma glucose at least 126 mg/dL, hemoglobin A1c above 6.5%, or administering hypoglycemic agents or insulin were defined as falling ill with diabetes. Cardiovascular disease was identified as self-reported physician-diagnosed heart attack or stroke, coronary heart disease. Cancer was identified by self-reported physician-diagnosed cancer.

Follow-Up and Mortality Data

Death certificate records of which relevant data are contained in the public-use linked mortality file for NHANES 1999–2004 are able to be linked to NHANES. And follow-up time defined by months, mortality status, and fundamental causes of mortality defined by Underlying Cause of Death 113 (UCOD_13) code category according to the International Classification of Diseases, 10th Revision (ICD-10) for deaths between 1999 and 2015 are included in the mortality file through December 31, 2015 [20]. We focused on 3 cause-specific deaths consisting of cardiovascular disease, cancer, and diabetes, among which the first item was considered as heart disease or cerebrovascular disease mortality. The duration of follow-up was 14 years for the participants in our study.

Statistical Analyses

The number (proportions) for categorical variables and the median (interquartile range) for non-normally distributed and continuous variables were applied to show the baseline characteristics of participants classified by presence of CKD and PN. Mann-Whitney U test and χ^2 test were adopted to compare the median and percentage according to any two out of four groups, respectively. And χ^2 test was adopted to make a comparison about the prevalence of PN in any two out of four groups classified as without CKD and diabetes, without CKD and with diabetes, with CKD and diabetes, and with CKD and without diabetes. Then we conducted Cox proportional hazard regressions adjusted potential demographic and clinical confounders to measured hazard ratios (HRs) and 95% confidence intervals (CIs), which was used to explore the relationship between PN and all-cause, cardiovascular-specific, cancer-specific, and diabetes-specific mortality in population with and without CKD separately. And Cox proportional hazard regressions were also conducted in order to compare the risk of mortality on PN across 4 groups classified as without CKD and PN, without CKD and with PN, with CKD and without PN, and with CKD and PN, according to which survival curve and log-rank test were adopted. Furthermore, a Wald test was used to be conducted stratified analyses to assess the association of PN and mortality in subgroups of potential influential variables. An interaction term between PN and the potential influential factor was established in the likelihood ratio test, of which the significance was measured. The management and analyses of all data were applied to conduct by R version 3.5.4.

Results

Characteristics

7,872 individuals were included in our research. And prevalence rates of PN were 28.4% (522/1,836) and 14.8% (893/6,036) in people with CKD and without CKD, respectively. Participants with PN were older, male, non-Hispanic white, married, with a lower education level, more history of comorbidities, and lower eGFR than those without PN in either CKD or no CKD population (Table 1). And the level of serum potassium ion concentration in population with CKD and PN was statistically significantly higher than in those with CKD and without PN, without CKD and with PN, and without CKD and PN. Moreover, the prevalence rate of PN in participants suffering from diabetes and CKD (40.3%)

Table 1. Baseline characteristics of the study population according to CKD and PN status

Characteristics	No CKD		CKD	
	no PN (*n* = 5,143)	PN (*n* = 893)	no PN (*n* = 1,314)	PN (*n* = 522)
Age, years	55.0 (47.0, 66.0)[a]	65.0 (54.0, 75.0)[b]	70.0 (59.0, 80.0)[c]	75.0 (66.0, 82.0)[d]
Male, *n* (%)	2,451 (47.7)[a]	567 (63.5)[b]	591 (45.0)[a]	315 (60.3)[b]
Self-reported race/ethnicity, *n* (%)				
Mexican American	1,085 (21.1)[a]	204 (22.8)[a]	232 (17.7)[a]	93 (17.8)[b]
Others	346 (6.7)[a]	50 (5.6)[a]	87 (6.6)[a]	28 (5.4)[a]
Non-Hispanic white	2,801 (54.5)[a]	469 (52.5)[a]	758 (57.7)[a]	309 (59.2)[a]
Non-Hispanic black	911 (17.7)[a]	170 (19.0)[a]	237 (18.0)[a]	92 (17.6)[a]
Married (%)	3,212 (62.5)[a]	529 (59.2)[a,b]	679 (51.7)[c]	274 (52.5)[b,c]
Education, *n* (%)				
Less than high school	1,535 (29.8)[a]	394 (44.1)[b]	503 (38.3)[c]	240 (46.0)[b]
High school graduates or equivalent	1,228 (23.9)[a]	204 (22.8)[a]	327 (24.9)[a]	104 (19.9)[a]
Some college or above	2,380 (46.3)[a]	295 (33.0)[b]	484 (36.8)[b]	178 (34.1)[b]
Family PIR level, *n* (%)				
≥4	1,663 (32.3)[a]	177 (19.8)[c]	300 (22.8)[c]	86 (16.5)[b]
>1–<4	2,812 (54.7)[a]	559 (62.6)[b]	825 (62.8)[b]	343 (65.7)[b]
≤1	668 (13.0)[a]	157 (17.6)[b]	188 (14.3)[b]	93 (17.8)[b]
Alcohol drinking, *n* (%)				
Nondrinkers	1,183 (26.6)[a]	253 (34.8)[b]	414 (38.8)[b,c]	178 (44.9)[c]
Moderate drinkers	1,859 (41.9)[a]	288 (39.6)[a]	419 (39.2)[a]	165 (41.7)[a]
Binge drinkers	945 (21.3)[a]	114 (15.7)[b]	161 (15.1)[b]	37 (9.3)[c]
Heavy drinkers	453 (10.2)[a]	72 (9.9)[a]	74 (6.9)[b]	16 (4.0)[b]
Cigarette smoking (%)				
Never smoking	2,410 (46.9)[a]	396 (44.4)[a]	613 (46.7)[a]	245 (46.9)[a]
Former smoking	1,654 (32.2)[a]	338 (37.9)[b]	488 (37.1)[b]	218 (41.8)[b]
Current smoking	1,071 (20.9)[a]	158 (17.7)[a,b]	213 (16.2)[b]	59 (11.3)[c]
>10 min of vigorous/moderate recreational activity per week, *n* (%)	2,891 (58.1)[a]	393 (47.3)[b]	587 (48.1)[b]	197 (44.3)[b]
BMI, kg/m^2	27.7 (24.6, 31.4)[a]	27.8 (25.0, 32.1)[a]	27.8 (24.3, 31.8)[a]	28.2 (25.4, 31.9)[a]
Total-to-HDL cholesterol ratio ≥5.9, *n* (%)	630 (12.2)[a]	110 (12.3)[a]	171 (13.0)[a]	58 (11.1)[a]
Prevalent hypertension, *n* (%)	2,286 (46.9)[a]	488 (57.3)[b]	967 (77.2)[c]	400 (79.8)[c]
Prevalent diabetes, *n* (%)	426 (8.5)[a]	149 (17.1)[b]	289 (22.6)[c]	191 (38.0)[d]
History of CVD, *n* (%)	568 (11.1)[a]	178 (20.0)[b]	371 (28.6)[c]	210 (40.6)[d]
History of cancer, *n* (%)	546 (10.6)[a]	127 (14.2)[b]	216 (16.5)[b,c]	107 (20.5)[c]
eGFR, mL/min per 1.73 m^2	92.5 (80.4, 104.2)[a]	89.2 (77.6, 100.8)[b]	63.1 (51.2, 90.6)[c]	58.3 (46.5, 83.3)[d]
ACR, mg/g	6.0 (4.1, 10.0)[a]	7.5 (4.8, 13.0)[b]	40.4 (12.5, 96.4)[c]	46.6 (15.6, 141.7)[c]
K, mmol/L	4.06 (0.33)[a]	4.11 (0.36)[b]	4.13 (0.43)[b]	4.23 (0.45)[c]
CKD stage, *n* (%)				
1	–	–	339 (25.8)[a]	91 (17.4)[b]
2	–	–	350 (26.6)[a]	141 (27.0)[a]
3	–	–	573 (43.6)[a]	249 (47.7)[a]
4	–	–	52 (4.0)[a]	41 (7.9)[b]

Categorical variables were given as number (percentage) and continuous variables as median with interquartile range due to their skewed distributions. Each superscript denotes a subset of different disease status (CKD/PN) whose column proportions do not differ significantly from each other at the 0.05 level. Details about the tests are described in method. CKD, chronic kidney disease; PN, peripheral neuropathy; PIR, income-poverty ratio; HDL, high-density lipoprotein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ACR, albumin-creatinine ratio; K, serum potassium.

was statistically significantly higher than that in both patients with CKD and without diabetes (24.1%) and patients without CKD and with diabetes (25.4%) (online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000535481).

Association between PN and Mortality

During 14 years of a median follow-up, 1,072 (58.4%) and 1,389 (23.0%) deaths were recorded in participants with CKD and without CKD, respectively. In crude Kaplan-Meier analyses, risks for all-cause, cardiovascular mortality, cancer

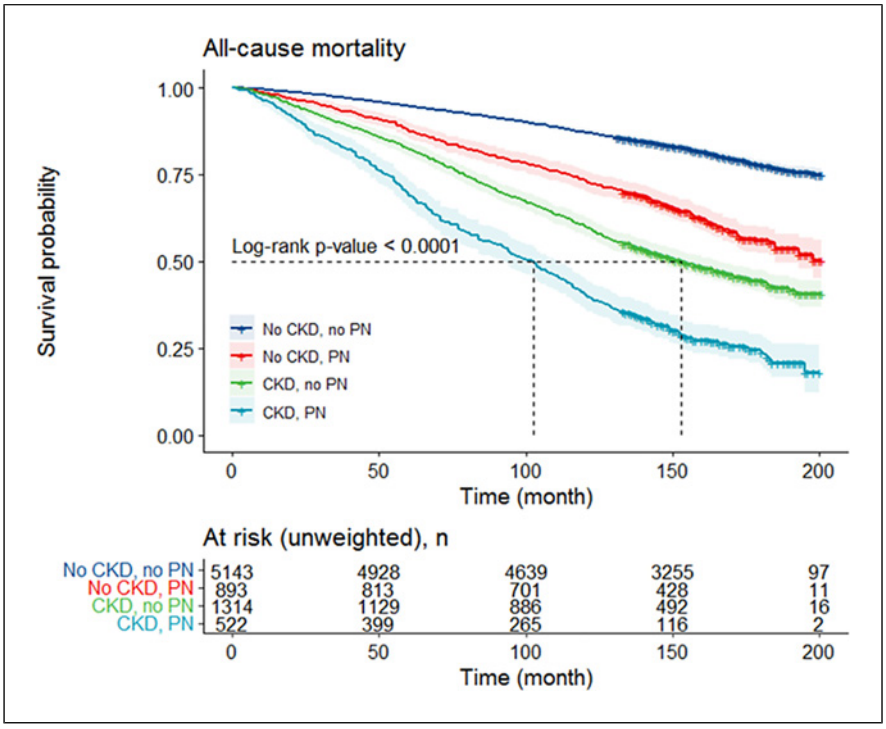

Fig. 2. Kaplan-Meier (crude) survival curves of all-cause mortality stratified by PN and CKD status.

mortality, and diabetes mortality were highest among adults with CKD and PN, when compared to other groups (Figure 2; online suppl. Fig. 2). The cumulative incidence of all-cause mortality among adults with CKD but no PN was higher than that for adults with PN but no CKD (Fig. 2).

The survival analysis was performed to detect the relationship between PN and mortality. Four groups were categorized to identify if there would be an excess growth on threats of all-cause mortality in the participants with CKD or/and PN. And an additional increase in all-cause mortality was observed in participants with PN and without CKD (HR: 1.33; 95% CI: 1.17–1.50), with CKD and without PN (HR: 1.56; 95% CI: 1.40–1.73), with both PN and CKD (HR: 1.96; 95% CI: 1.72–2.23) in the multivariable model, compared to those without PN and CKD (Table 2).

In addition, two groups were classified based on CKD, where we analyzed the association of PN and mortality, respectively (Table 3). PN was found to be related to the all-cause mortality in both CKD group (HR: 1.34; 95% CI: 1.17–1.53) and non-CKD group (HR: 1.27; 95% CI: 1.12–1.43). Participants with PN were at a 42% higher risk of cardiovascular mortality (HR: 1.42; 95% CI: 1.07–1.90) and a 91% higher diabetes mortality (HR: 1.91; 95% CI: 1.14–3.18) after adjusting multivariable compared to those without PN in population with CKD. Nevertheless, the relationships of PN and risks of cardiovascular and diabetes mortality were not significantly demonstrated in the group of non-CKD when considering all confounders (HR: 1.23; 95% CI: 0.91–1.67; HR: 0.66; 95% CI: 0.25–1.75, respectively). The association between PN and cancer mortality was not statistically significant in both CKD and non-CKD group.

Subgroup Analyses

In Figure 3 and online supplementary Figures 3, 4, and 5, participants were classified by some factors considered containing potential impacts on all-cause mortality in the presence of PN and analyzed for the mortality risk with PN in each subgroup. Figure 1 showed that individuals with lower BMI, current smoking, being in CKD stage 2 and higher ACR in CKD group tended to have stronger positive relationships between PN and all-cause mortality compared to those with higher BMI, no current smoking, being in CKD stage 4 and lower ACR in CKD group (p for trend is <0.001, <0.001, <0.001 and 0.013 in each subgroup, respectively). Difference in all-cause mortality when comparing PN to no PN in participants with diabetes and those without diabetes, all of which were with CKD, was not found significant, while that in cardiovascular- and diabetes-related mortality was found significant (online suppl. Figures 3 and 5). And only individuals with higher age were found to have statistically stronger positive relationships between PN and all-cause mortality in subgroups consisting of population without CKD.

Table 2. Associations of PN status or CKD status with all-cause mortality

	Age, gender, race-adjusted model		Multivariable model*	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
PN				
PN−	Ref		Ref	
PN+	1.39 (1.28, 1.52)	<0.001	1.34 (1.20, 1.44)	<0.001
CKD				
CKD−	Ref		Ref	
CKD+	1.81 (1.66, 1.98)	<0.001	1.53 (1.40, 1.67)	<0.001
PN CKD				
PN− CKD−	Ref		Ref	
PN+ CKD−	1.42 (1.26, 1.60)	<0.001	1.33 (1.17, 1.50)	<0.001
PN− CKD+	1.85 (1.67, 2.04)	<0.001	1.56 (1.40, 1.73)	<0.001
PN+ CKD+	2.35 (2.07, 2.66)	<0.001	1.96 (1.72, 2.23)	<0.001

HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; PN, peripheral neuropathy; eGFR, estimated glomerular filtration rate; ACR, albumin-creatinine ratio; BMI, body mass index; HDL, high-density lipoprotein. *Adjusted covariates: age, gender, race, family income-poverty ratio level, education level, marital status, alcohol consumption, smoking status, leisure-time physical activity, baseline eGFR, ACR, BMI, total-to-HDL cholesterol ratio, serum potassium, hypertension, diabetes, cardiovascular disease, and cancer.

Table 3. Associations of PN status with all-cause mortality stratified by CKD or non-CKD*

PN	No CKD		CKD	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
All-cause mortality				
PN−	Ref		Ref	
PN+	1.27 (1.12, 1.43)	<0.001	1.34 (1.17, 1.53)	<0.001
Cardiovascular mortality				
PN−	Ref		Ref	
PN+	1.23 (0.91, 1.67)	0.171	1.42 (1.07, 1.90)	0.016
Cancer mortality				
PN−	Ref		Ref	
PN+	1.10 (0.86, 1.42)	0.443	1.18 (0.86, 1.63)	0.305
Diabetes mortality				
PN−	Ref		Ref	
PN+	0.66 (0.25, 1.75)	0.404	1.91 (1.14, 3.18)	0.013

HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; PN, peripheral neuropathy; eGFR, estimated glomerular filtration rate; ACR, albumin-creatinine ratio; BMI, body mass index; HDL, high-density lipoprotein. *Adjusted covariates: age, gender, race, family income-poverty ratio level, education level, marital status, alcohol consumption, smoking status, leisure-time physical activity, baseline eGFR, ACR, BMI, total-to-HDL cholesterol ratio, serum potassium, hypertension, diabetes, cardiovascular disease, and cancer.

Discussion

A high prevalence of PN in participants suffering from CKD, even among CKD patients without diabetes, was found in our research which was longitudinal nationally representative. PN was strongly related to the risk of all-cause mortality (mainly from cardiovascular- and diabetes-related mortality) in individuals with CKD. Even adjusted for prevalent cardiovascular disease and potential confounding variables, the relationship of PN and mortality in participants with CKD persisted. Overall, our data suggested that PN in patients with CKD may be able to predict poor outcomes.

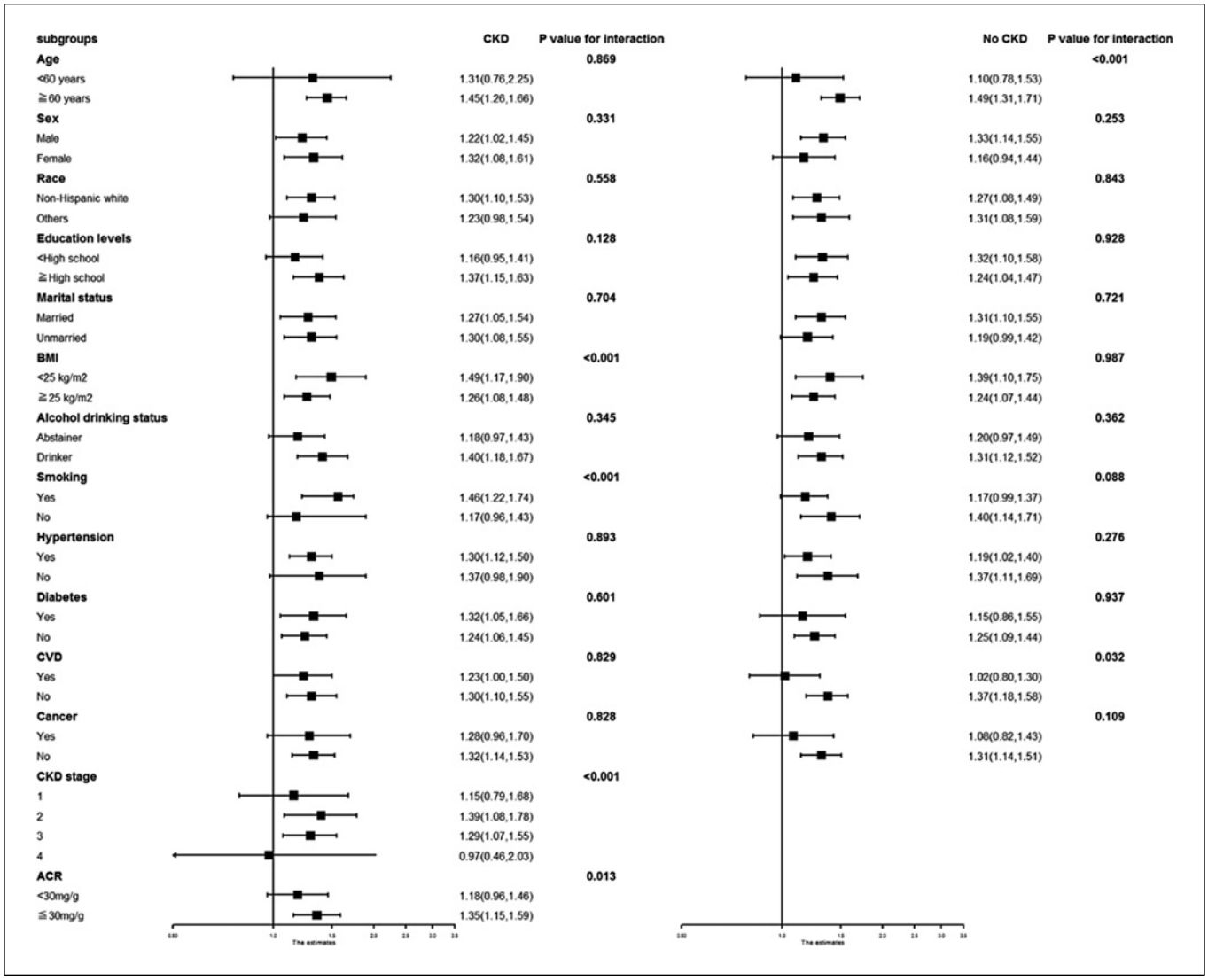

Fig. 3. Subgroup analyses of the associations between PN and all-cause mortality. Adjusted covariates: age, gender, race, family income-poverty ratio level, education level, marital status, alcohol consumption, smoking status, leisure-time physical activity, baseline eGFR, ACR, BMI, total-to-HDL cholesterol ratio, serum potassium, hypertension, diabetes, cardiovascular disease, and cancer. CKD, chronic kidney disease; PN, peripheral neuropathy; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ACR, albumin-creatinine ratio; BMI, body mass index; HDL, high-density lipoprotein.

We found a prevalence of 28.4% for PN among CKD patients and 24.1% for PN among nondiabetic CKD patients. Although diabetes is thought to be a recognized factor for the progress risk of PN, the high prevalence of PN in the CKD population without diabetes is noteworthy. And CKD was found significantly associated with the prevalence of PN regardless of the presence or absence of diabetes in our research, which was consistent with the finding of Arnold et al. [21] showing an elevated prevalence of PN in the CKD population, even in patients with early-stage CKD and without diabetes. Also, one study found that CKD patients with diabetes develop more severe length-dependent neuropathy than CKD patients without diabetes [22], which suggested that diabetes and CKD may act together as synergistic factors in the disease process of PN. We suggest that further studies on the subgroup of severity of PN could be initiated in the CKD population.

PN in CKD patients was found to be related to higher all-cause mortality (mainly from cardiovascular- and diabetes-related mortality). However, in terms of cardiovascular mortality, a higher risk was not observed significantly in non-CKD participants with PN than that in non-CKD

participants without PN. The effect of PN on mortality has been found to be contributory in studies of the general population over 40 years old [23]. Notably, research on impacts of PN on mortality is absent in CKD patients. Previous studies revealed that PN in adults was related to a higher incidence of new-onset vascular occurrences (diabetic retinopathy, ischemic stroke/transient ischemic attack, coronary artery disease) [24], suggesting that the presence of PN may reflect systemic subclinical microvascular disease [24, 25]. According to our findings, CKD patients with PN demonstrated inferior renal function levels and a diminished eGFR when compared to CKD patients without PN. This observation suggests that PN may serve as an indicative parameter for the progression of glomerular microangiopathy and the decline in renal function among CKD patients, ultimately contributing to the development of end-stage renal disease and eventual mortality.

We found that PN tends to amplify the threat of mortality in CKD individuals by increasing a cardiovascular burden, among which there was accumulating evidence of possible mechanisms. First, cardiac autonomic neuropathy, one of the neurological complications of CKD which was pervasive, complex, and systemic and included cognitive impairment, stroke, restless leg syndrome, mononeuropathy, myopathy, and peripheral and autonomic neuropathy [4], is an explicable cause. When uremia toxins lead to neuropathy, manifesting as length-dependent polyneuropathy involved myelinated fiber (i.e., PN), the toxins are also contributed to demyelinating polyneuropathy [26, 27], which leads to cardiac autonomic neuropathy. And cardiac autonomic neuropathy is associated with life-threatening conditions [28–30]. A correlation between autonomic nerve damage and sudden cardiac death has been reported in patients awaiting renal transplantation [31, 32]. The second reason is considered to be hyperkalemia. One study showed a causal relationship between elevated potassium ions and reduced neuro-excitability in individuals with end-stage renal disease [33]. Moreover, a small RCT trial demonstrated that low potassium slowed the increase in total neuropathy score (TNS) [5]. Hyperkalemia, while causing PN, may also involve the heart and induce lethal arrhythmias. Taken together, the pathophysiological pathways that lead to the emergence of PN due to CKD may induce fatal cardiac event.

The lack of a significant effect of diabetes on the association between PN and the mortality risk in patients with CKD warrants further discussion. In population with CKD, the risk of all-cause mortality on PN in the subgroup with diabetes was comparable to that in the subgroup without diabetes. In other words, PN was an independent risk factor for all-cause mortality in CKD population with or without diabetes. And the risks of cardiovascular and diabetes mortality on PN in CKD populations with diabetes were higher compared with those in CKD populations without diabetes. It has been shown that the hyperglycemic state can lead to neuropathy by decreasing NO utilization and altering the prostaglandin profile, which in turn increases neurovascular constriction, leading to inadequate neural blood supply [34]. At the same time, the superimposed uremic state and its unique metabolic and physiological alterations further exacerbate the deterioration of PN cause by diabetes [34, 35], which leads to various neurological sequelae. A higher risk of mortality in diabetes individuals with neurological sequelae (e.g., foot ulcers) than in diabetes patients without neurological sequelae was reported, which was mainly attributed to subsequent major amputations or a higher prevalence of large vessel atherosclerotic disease in the population affected by neurological sequelae [36, 37]. Thus, higher risks of cardiovascular mortality on PN in CKD population with DM may be partly attributable to major amputations and vascular disorders exacerbated by CKD and diabetes together. In conclusion, as an under-recognized risk factor, the pathogenesis and adverse prognostic effects of PN in the CKD population are of concern and may be an important target for intervention.

The merit in our research included a large sample size used to observe the effect of PN on the risk of death in the CKD cohort and the exploration of the influence of diabetes on risks of death associated with PN in the CKD cohort. The weaknesses of our study are as below. First, the PN was measured using monofilament sensitivity, which is not as quantitatively indicative of severity as total neuropathy score (TNS) for PN, though it may be more clinically practicable because of the simplicity of its qualitative examination than the usual clinical care routines for these patients. Second, our investigation is an observational study and lacks strength in the demonstration of causality. Third, the exploration of diabetes was conducted in an exploratory subgroup analysis, and the reliability of the results of which was poorer than in a confirmatory subgroup analysis. Fourth, participants in our study may receive measures to alleviate PN during the follow-up period; however, such information was not included in the follow-up content, which may interfere somewhat with the results of the study.

Conclusion

A higher prevalence of PN in population with CKD was found in our study than in the population without CKD. The CKD patients with diabetes were also facing higher incidence of PN than in non-CKD patients with diabetes. And PN was found to be related to a higher risk of all-cause and cardiovascular mortality in the CKD

patients, which clinically suggests the adverse prognostic impact of PN in the CKD population is of concern and may be an important candidate for intervention.

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Statement of Ethics

Since the current study was a secondary analysis of NHANES data, which are publicly available, no Institutional Review Board approval was necessary or obtained.

Conflict of Interest Statement

All authors declare no conflict of interest.

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Author Contributions

Conceptualization: Gang Xu; data curation, formal analysis, and writing – original draft: Wei-Lan Li and Xiao-Yu Cai; methodology and writing – review and editing: Shu-Wang Ge; resources and software: Xiao-Yu Cai; and validation: Wei-Lan Li. Wei-Lan Li and Xiao-Yu Cai contributed equally to the article.

Data Availability Statement

The data that support the findings of this study are openly available in National Center for Health Statistics at https://www.cdc.gov/nchs/nhanes/index.htm. Further inquiries can be directed to the corresponding author.

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