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CLINICAL STUDY

Mediated roles of oxidative stress and kidney function to leukocyte telomere length and prognosis in chronic kidney disease

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ABSTRACT

Background: Few studies have focused on the correlation between leukocyte telomere length (LTL) and cancer-related mortality or identified potential factors that mediate the relationship between LTL and mortality among chronic kidney disease (CKD) patients. Our study aimed to explore the associations between LTL and all-cause and cause-specific mortality and to identify the underlying mediators.

Methods: CKD patients were obtained from the National Health and Nutrition Examination Survey (NHANES) 1999–2002. Cox regression analysis and restricted cubic spline analysis were used to explore the associations between LTL and all-cause or specific-cause mortality and their nonlinear connections. Stratified analyses were executed to assess the relationships among the different subgroups. The latent mediated factors were confirmed using mediation analysis. Sensitivity analyses were used to evaluate the robustness of our findings.

Results: Longer LTL associated with the lower risk of all-cause mortality, cardiovascular disease (CVD) and cancer-related mortality, and U-shaped relationships were detected. Patients younger than 65 years with greater LTL or who had hypertension had better prognoses. Age and history of hypertension were associated with LTL and overall mortality. In addition, estimated glomerular filtration rate (eGFR), albumin, and total bilirubin mediated the association, and the proportions of indirect effects were 7.81%, 3.77%, and 2.50%, respectively. Six sensitivity analyses confirmed the robustness of our findings.

Conclusions: This study revealed that LTL was a protective factor for survival among patients with CKD and emphasized the mediating roles of oxidative stress and kidney function.

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Leukocyte telomere length; chronic kidney disease; survival; oxidative stress; NHANES

Introduction

Chronic kidney disease (CKD) is a severe kidney disorder in which kidney function gradually worsens. Approximately, 750 million individuals are troubled by this disease worldwide because of the increasing age of the population [1]. Although the number of deaths has decreased in patients with end-stage CKD [2], CKD is regarded as a significant cause of death worldwide according to research on the global burden of disease [3]. It is predicted that CKD will become the fifth cause of death globally by 2040 [4]. Compared with other organs, the kidney shows the most obvious changes associated with age. The senescence of the kidney is a complicated and multistep process, and renal function and structure become more aggravated [5]. There is an urgent need to find valid biomarkers to predict the mortality of CKD patients to improve their life expectancy and quality through more rational management.

Telomeres are located at the ends of chromosomes and prevent DNA damage from occurring [6,7]. In general, the length of telomeres decreases during cell division. As a result, extremely short telomeres contribute to cell apoptosis as well as senescence [8]. A shorter telomere length attenuated the ability to restore telomeres after acute kidney injury occurred [9]. Telomere length is closely related to aging-related diseases, such as cardiovascular disease (CVD), diabetes mellitus (DM), and cancer. There is an intimate link between leukocyte telomere length (LTL) and telomere length among the cells of internal organs such as the kidney [10–12]. LTL also has a positive relationship with survival, similar to telomere length in several diseases [13,14].

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Many studies have demonstrated that shorter LTLs are associated with an increased risk of CKD progression [15–19]. Patients with shorter LTLs had higher serum creatinine (Scr) levels [17]. However, few studies have focused on the association between LTL and mortality among CKD patients, and the results are confusing. LTL shortening was correlated with worse survival in multivariate analysis but not in univariate analysis based on a French study [18]. Moreover, a German study demonstrated that LTL was a valid marker of all-cause and CVD-related death in patients with moderate CKD and that LTL was related to a decreased estimated glomerular filtration rate (eGFR) [20]. An effective marker for CKD therefore may be LTL. However, another study revealed that reduced LTL was not negatively related to mortality in CKD patients [21]. More studies are needed to confirm the possible associations between these factors in patients with CKD. In addition, CKD exacerbates the inflammatory response and damages the immune system, which might subsequently lead to increased cancer risk [22,23]. Individuals who experience CKD have a greater risk of mortality than healthy people do [24]. One study involving Americans with CKD suggested that the proportion of patients who died from cancer was approximately 32% [25]. LTL shortening was correlated with kidney dysfunction in the population [26]. In addition, researchers have shown that oxidative stress is highly important for destroying kidney function and shortening the LTL [27]. Oxidative stress is normal in CKD patients and is a trigger for increased LTL attrition [28]. However, previous clinical studies reported a relationship between LTL and mortality but did not explore the potential effects on kidney function and oxidative stress.

Therefore, we hypothesized that LTL might affect mortality through senescence, oxidative stress, or renal function. Therefore, our study aimed to explore the latent link between LTL and all-cause, cardiovascular-related and cancer-related mortality and to identify the underlying mediators among them in patients with CKD from the US.

Methods

Study population

This was a retrospective cohort study. The database was obtained retrospectively from the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2002. The NHANES is a nationally representative cross-sectional survey periodically conducted in the United States by the National Centre for Health Statistics and employs a stratified multistage random sampling design. All enrolled patients signed written informed consent forms, and the process was censored and ratified by the National Centre for Health Statistics Research Ethics Review Board (NCHS ERB) (https://www.cdc.gov/nchs/nhanes/about/erb.html).

We identified 20,961 potential participants. The inclusion criterion was CKD patients who were older than 20 years. The exclusion criteria were as follows: (a) younger than 20 years, (b) did not have CKD, and (c) missing follow-up data. According to the inclusion and exclusion criteria, 1,737 participants were ultimately enrolled. A total of 19,224 respondents were excluded from the study, of whom 18,435 individuals did not have CKD, 788 individuals were younger than 20 years, and one respondent had missing data during follow-up. The detailed screening procedure is shown in Figure 1.

Definition of CKD

CKD was identified according to the KDIGO 2024 Clinical Practice Guideline [29]. The urinary albumin–creatinine ratio (UACR) was separated into three classes: A1 (<30 mg/g), A2 (30–300 mg/g), and A3 (>300 mg/g). The eGFR was grouped into G1, G2, G3, G4, and G5 based on five levels: ≥90 mL/min/1.73 m^2; 60–89 mL/min/1.73 m^2; 30–59 mL/min/1.73 m^2; 15–29 mL/min/1.73 m^2; and <15 mL/min/1.73 m^2. In brief, adults were regarded as having CKD if their eGFR was <60 mL/min/1.73 m^2 or if their ACR was >30 mg/g [30,31].

Measurements of LTL

In the laboratory portion of the NHANES interview, LTL was measured. Polymerase chain reaction was used to evaluate telomere length. The relative ratio against standard reference DNA (T/S) was determined through calculation. The base pairs were modified for analysis using information from previous research [32,33]. The detailed information is shown on the NHANSE website (https://www.cdc.gov/nchs/nhanes/index.htm).

Other covariates

We collected data on age, sex, race, marital status, education, the income-to-poverty ratio (PIR), body mass index (BMI), alcohol use, and smoking status from the demographic information

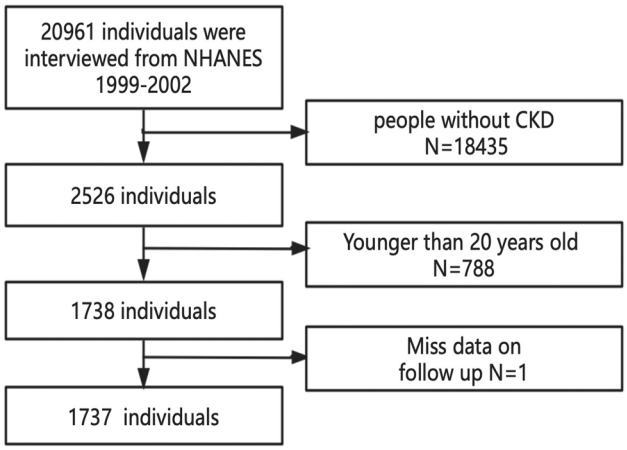

Figure 1. Flowchart of the population in this study.

section. The history of hypertension and DM was based on questionnaire data. Other covariates were collected from the examination information section. Gamma glutamyl transferase (GGT, IU/L), albumin (Alb, g/L), and total bilirubin (TB, μmol/L) were used as markers of oxidative stress according to previous studies [34,35]. The eGFR (mL/min), Scr (mg/dL), uric acid (mg/dL), and blood urea nitrogen (BUN, mg/dL) are considered markers of renal function. C-reactive protein (CRP, mg/dL), lymphocyte number (LYM, $\times 10^3$ cells/μL), white blood cells (WBCs, $\times 10^3$ cells/μL), high-density lipoprotein cholesterol (HDL-C, mmol/L), low-density lipoprotein cholesterol (LDL-C, mmol/L), red blood cells (RBCs, $\times 10^3$ cells/μL), and hemoglobin (Hb, g/dL) were also collected because they are reportedly related to prognosis or kidney function in CKD patients.

Ascertainment of mortality

The follow-up in this study ended on 31 December 2019. Death from any cause was defined as all-cause mortality. CVD (I00–I09, I11, I13, I20–I51, I60–I69), cancer (C00–C97), DM (E10–E14), chronic lower respiratory diseases (J40–J47), Alzheimer's disease (G30), nephritis, nephrotic syndrome and nephrosis (N00–N07, N17–N19, N25–N27), accidents (unintentional injuries) (V01–X59, Y85–Y86), and influenza and pneumonia (J09–J18) were categorized according to the International Statistical Classification of Diseases and Related Health Issues (ISCDRH).

Statistical methods

Sample weights were considered in our study in accordance with the NCHS analytic guidelines. All methods in this study were performed in accordance with the relevant guidelines and regulations on the NHANES website. Missing data were supplemented by multiple imputation. Continuous variables and categorical variables are described as the means (standard errors) and numbers (percentages), respectively. The levels of LTL were divided into tertiles, and the ranges of LTL at T1, T2, and T3 were [0.43, 0.81], (0.81, 1.00], and (1.00, 3.00], respectively. *T* tests, Mann–Whitney's *U*-tests, and Chi-square tests were used to compare normally distributed data, non-normally distributed continuous data, and categorical variables, respectively.

The associations between LTL and all-cause or specific-cause mortality were explored via Cox regression analysis with three models. No adjustments for covariates were made in model 1. Model 2 was modified to account for age, sex, ethnicity, PIR smoker, alcohol use, hypertension, DM, and BMI. Model 3 was additionally modified by taking into account the levels of Alb, TB, CRP, eGFR, Scr, uric acid, BUN, HDL-C, LDL-C, GGT, LYM, and Hb and WBC and RBC counts. Additionally, prognostic differences among the three levels of LTL were estimated using Kaplan–Meier's analysis and the log-rank test. The nonlinear connection was evaluated using restricted cubic spline (RCS) analysis. Stratified analyses were executed to assess the variances among different subgroups. The latent factors mediating the association between LTL and mortality were identified via mediating effect analysis. Finally, the robustness of our findings was evaluated by executing six sensitivity analyses in this research. The first sensitivity analysis was executed after excluding individuals who died within 2 years of follow-up. The second sensitivity analysis excluded individuals with cancer. The third sensitivity analysis did not adjust for NHANES survey weights. The fourth and fifth sensitivity analyses involved dividing individuals into two groups by LTL or considering LTL as a continuous variable. The sixth sensitivity analysis included individuals younger than 20 years.

The analyses mentioned above were conducted using R (version 4.3.3) (R Foundation for Statistical Computing, Vienna, Austria) and R Studio (Boston, MA). The R packages used included 'rms', 'survey', and 'ggplot2'. A p value less than .05 was considered statistically significant.

Results

Baseline characteristics of patients with CKD from NHANES 1999–2002

Among the enrolled patients, the median age was 59.60 years, and 42.14% were men. Most patients (83.06%) were non-Hispanic White or Black, and 19.87% were smokers (Table 1). A shorter LTL was associated with a reduced eGFR and RBC and increased Scr, uric acid, and BUN, which suggested that LTL might be related to kidney function (all p values <.05). There were 33.32%, 21.44%, 38.53%, 1.63%, and 1.72% patients with CKD stages 1–5, respectively. Patients with lower CKD stages had greater LTLs.

Moreover, a total of 1,142 patients died at the end of follow-up. The two leading causes of death were CVD (19.63%) and malignant neoplasms (8.53%). Other causes were DM (2.62%), chronic lower respiratory diseases (2.45%), Alzheimer's disease (2.43%), nephritis, nephrotic syndrome or nephrosis (1.80%), accidents (1.75%), influenza and pneumonia (1.14%), and others (13.65%). Patients with greater LTLs tended to have better survival ($p < .001$) (Table S1).

Associations between all-cause, cardiovascular-related and cancer-related mortality among CKD patients

Table 2 shows that the risk of all-cause mortality decreased with increasing LTL according to the three Cox regression models. After adjustment for covariates in model 3, all-cause death was lower in those in the second tertile (HR = 0.66, 95% CI = 0.54–0.80) and third tertile (HR = 0.59, 95% CI = 0.47–0.73) than in those in the lowest tertile. Moreover, LTL was also a protective factor against CVD- and cancer-related mortality. The HRs and 95% CIs were 0.57 (0.41–0.81) in the T2 subgroup and 0.50 (0.34–0.72) in the T3 subgroup in model 3 for CVD mortality. For cancer-related mortality, death rates declined by 55% and 64% in the T2 and T3 groups, respectively. The survival curves in Figure 2 show that the risk of death, CVD and cancer-related mortality decreased with increasing LTL (all p values <.001).

Table 1. The baseline characteristics of patients with CKD.

Variables	Total	T1 [0.43, 0.81)	T2 (0.81, 1.00]	T3 (1.00, 3.00]	*p* Value
Age (years)	59.60 (0.82)	70.32 (0.84)	61.83 (1.31)	50.12 (1.49)	**<.001**
Sex					.350
Men	812 (42.14%)	297 (44.18%)	273 (43.42%)	242 (39.61%)	
Women	925 (57.86%)	281 (55.82%)	307 (56.58%)	337 (60.39%)	
Ethnicity					**.030**
Mexican American	340 (5.00%)	108 (3.42%)	113 (5.01%)	119 (6.11%)	
Non-Hispanic White or Back	1267 (83.06%)	445 (91.13%)	418 (81.70%)	404 (78.51%)	
Other race/multiracial	130 (11.94%)	25 (5.45%)	49 (13.29%)	56 (15.38%)	
Smoker					**.010**
No	1,452 (80.13%)	508 (86.44%)	482 (80.54%)	462 (75.33%)	
Yes	285 (19.87%)	70 (13.56%)	98 (19.46%)	117 (24.67%)	
Alcohol user					**.030**
No	913 (48.37%)	319 (54.20%)	308 (49.88%)	286 (42.96%)	
Yes	824 (51.63%)	259 (45.80%)	272 (50.12%)	293 (57.04%)	
Hypertension					**<.001**
No	514 (37.61%)	145 (28.39%)	158 (35.32%)	211 (46.08%)	
Yes	1,223 (62.39%)	433 (71.61%)	422 (64.68%)	368 (53.92%)	
DM					.270
No	1,193 (74.29%)	391 (70.91%)	393 (74.85%)	409 (76.22%)	
Yes	544 (25.71%)	187 (29.09%)	187 (25.15%)	170 (23.78%)	
PIR	2.48 (0.09)	2.44 (0.11)	2.47 (0.11)	2.50 (0.15)	.930
BMI (kg/m^2)	29.13 (0.34)	28.97 (0.30)	29.53 (0.48)	28.92 (0.70)	.560
HDL-C (mmol/L)	1.31 (0.02)	1.29 (0.02)	1.29 (0.02)	1.33 (0.03)	.370
LDL-C (mmol/L)	3.15 (0.03)	3.15 (0.05)	3.09 (0.05)	3.19 (0.05)	.330
eGFR	74.00 (0.87)	62.86 (1.26)	70.25 (1.75)	84.92 (1.82)	**<.001**
Scr (mg/dL)	1.09 (0.03)	1.15 (0.05)	1.14 (0.07)	0.99 (0.03)	**.020**
Uric acid (mg/dL)	5.98 (0.07)	6.27 (0.09)	5.95 (0.09)	5.82 (0.10)	**.001**
BUN (mg/dL)	17.80 (0.20)	19.33 (0.32)	17.84 (0.45)	16.68 (0.41)	**<.001**
Alb (g/L)	42.54 (0.16)	42.20 (0.16)	42.51 (0.23)	42.81 (0.26)	.100
TB (μmol/L)	11.17 (0.19)	11.57 (0.40)	11.21 (0.37)	10.86 (0.19)	.270
GGT (IU/L)	37.57 (1.92)	40.67 (5.32)	37.43 (3.55)	35.50 (1.97)	.690
CRP (mg/dL)	0.62 (0.03)	0.65 (0.05)	0.70 (0.05)	0.53 (0.05)	**.050**
LYM (×10^3 cells/μL)	2.04 (0.02)	2.02 (0.03)	1.99 (0.04)	2.08 (0.06)	.490
WBC (×10^3 cells/μL)	7.45 (0.09)	7.47 (0.12)	7.44 (0.11)	7.44 (0.15)	.980
RBC (×10^6 cells/μL)	4.63 (0.03)	4.57 (0.03)	4.63 (0.03)	4.67 (0.04)	**.004**
Hb (g/dL)	14.15 (0.09)	14.13 (0.10)	14.17 (0.10)	14.14 (0.11)	.920
CKD stage					**<.001**
G1	465 (33.32%)	82 (16.93%)	145 (31.33%)	238 (48.90%)	
G2	395 (21.44%)	120 (20.92%)	136 (22.25%)	139 (22.99%)	
G3	744 (38.53%)	321 (58.37%)	256 (42.87%)	167 (24.93%)	
G4	43 (1.63%)	19 (2.65%)	9 (0.98%)	15 (1.61%)	
G5	37 (1.72%)	11 (1.12%)	16 (2.57%)	10 (1.57%)	
UACR classes					**<.001**
A1	480 (26.89%)	201 (38.18%)	173 (29.18%)	106 (17.04%)	
A2	1,007 (61.39%)	294 (52.01%)	320 (58.31%)	393 (70.57%)	
A3	250 (11.7%2)	83 (9.81%)	86 (12.51%)	81 (12.39%)	

T1: tertile 1; T2: tertile 2; T3: tertile 3; DM: diabetes mellitus; PIR: household poverty-to-income ratio; BMI: body mass index; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; Scr: serum creatinine; BUN: blood urea nitrogen; Alb: albumin; TB: total bilirubin; GGT: gamma glutamyl transferase; CRP: C-reactive protein; LYM: lymphocyte number; WBC: white blood cells; RBC: red blood cells; Hb: hemoglobin.

Data were presented as mean (SD) or *n* (%) after adjusted for NHANES survey weights. Bold *p*-values indicate statistical significance ($p < 0.05$).

According to the RCS analysis, LTL had a U-shaped connection with all-cause death (*p* for nonlinearity <.001), cardiovascular mortality (*p* for nonlinearity = .011), and cancer-related death (*p* for nonlinearity <.001) (Figure 3). All-cause mortality declined at the early stage until the LTL reached 1.036 and then rose when the LTL increased. Furthermore, the checkpoint effects of LTL on cardiovascular mortality and cancer-related mortality were 1.066 and 1.045, respectively.

Stratified analyses

Model 3 stratified analyses revealed that patients aged younger than 65 years with shorter LTLs and who had hypertension had a worse survival, as shown in Figure 4. Age (*p* for interaction = .004) and history of hypertension (*p* for interaction = .003) had interactions between LTL and all kinds of mortality. A history of smoking (*p* for interaction = .03) and DM (*p* for interaction = .04) interacted with the relationship between LTL and CVD death (Figure S1). Patients who did not smoke or who did not have DM with a greater LTL had better survival. With respect to cancer-related mortality, short LTL was associated with an obviously increased risk of cancer mortality regardless of age, sex, history of smoking, hypertension, and DM (all *p* values for interactions >.05) (Figure S2).

Mediation analysis

The mediation analysis revealed that age was the most important mediating factor linking LTL to all-cause mortality, and the mediation proportion was 85.67% (Figure 5(A)). Furthermore, eGFR

Table 2. The association between LTL and all-cause mortality.

	Model 1		Model 2		Model 3	
Character	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
All-cause						
T1	–		–		–	
T2	0.56 (0.44–0.71)***	<.001	0.69 (0.59–0.81)***	<.001	0.66 (0.54–0.80)***	<.001
T3	0.31 (0.24–0.39)***	<.001	0.60 (0.49–0.75)***	<.001	0.59 (0.47–0.73)***	<.001
CVD						
T1	–		–			
T2	0.48 (0.33–0.69)***	<.001	0.56 (0.41–0.76)***	<.001	0.57 (0.41–0.81)***	.001
T3	0.19 (0.12–0.30)***	<.001	0.48 (0.31–0.73)***	<.001	0.50 (0.34–0.72)***	<.001
Cancer						
T1	–		–			
T2	0.41 (0.26–0.67)***	<.001	0.43 (0.29–0.65***	.001	0.45 (0.28–0.71)***	<.001
T3	0.15 (0.09–0.24)***	<.001	0.33 (0.19–0.56)***	<.001	0.34 (0.19–0.61)***	<.001

T1: tertile 1; T2: tertile 2; T3: tertile 3; CVD: cardiovascular disease; HR: hazard ratio; CI: confidence interval.
Data were adjusted for NHANES survey weights. Model 1 was unadjusted. model 2 was modified for age, sex, ethnicity, PIR smoker, alcohol user, hypertension, DM, and BMI based on model 1. Model 3 was further adjusted for Alb, TB, CRP, eGFR, Scr, uric acid, BUN, HDL-C, LDL-C, GGT, LYM, WBC, RBC, and Hb.
***$p < 0.001$.

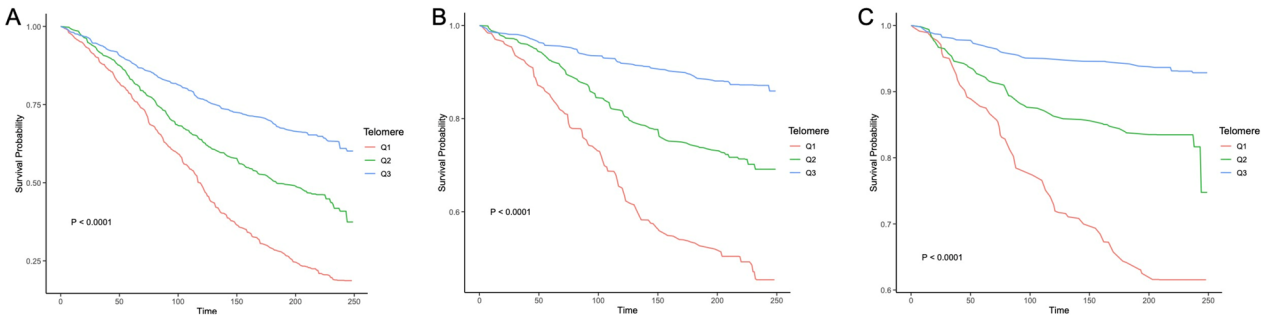

Figure 2. The Kaplan–Meier curves for the relationship between LTL with all-cause and cause-specific mortality. (A) All-cause mortality, (B) cardiovascular death, and (C) cancer-caused mortality.

($p < .001$, Figure 5(B)), Alb ($p = .020$, Figure 5(C)), and TB ($p = .040$, Figure 5(D)) mediated the association, and the percentages of indirect effects were 7.81%, 3.77%, and 2.50%, respectively.

Sensitivity analyses

Sensitivity analyses were conducted to evaluate the robustness of our findings. The findings remained robust after excluding individuals who died within 2 years of follow-up (Table 3), excluding individuals with cancer (Table S2), or not adjusting for NHANES survey weights (Table S3). The relationship did not visibly change after individuals were divided into two groups according to LTL (Table S4), LTL was treated as a continuous variable (Table S5), or individuals younger than 20 years were included (Table S6). Although there was no statistical significance for cancer-related death in the fifth sensitivity analysis, the HR still declined in the greater LTL group.

Discussion

In accordance with previous studies, our investigation revealed that a greater LTL was associated with a lower risk of all-cause mortality [36]. However, another study revealed that LTL had no negative association with the risk of mortality in CKD patients [21]. The reasons for these different results might be the evaluation methods used for LTL. This study [21] used the terminal restriction fragment (TRF) method, whereas we used quantitative PCR. TRF provided high-resolution measurements of individual telomeres, but it was less suitable for large-scale epidemiological studies [37]. LTL was measure through qPCR in NHANES database, which allowed us to analyze efficiently. More studies were considered by TRF analysis to further validate our findings to provide more detailed and biologically relevance. The abnormal function and length of telomeres are critical disadvantages of lifespan and organ senescence [38]. Telomeres gradually shorten during the process of cell division [38]. Finally, senescence or apoptosis occurs when the LTL is extremely short by activating the p53–p21 pathway and destroying the DNA structure [39]. In addition, LTL is modified by telomerase, which maintains the length of the telomere and prevents its shortening [40]. A greater LTL is known to be associated with renal dysfunction, which has been genetically characterized [41–44]. Reduced LTL is related to increased survival [36]. However, a few studies have described this tendency in patients with non-dialysis-dependent kidneys [16,45]. Whether LTL could become a useful biomarker for the prognosis of CDK patients is controversial. Possible reasons for

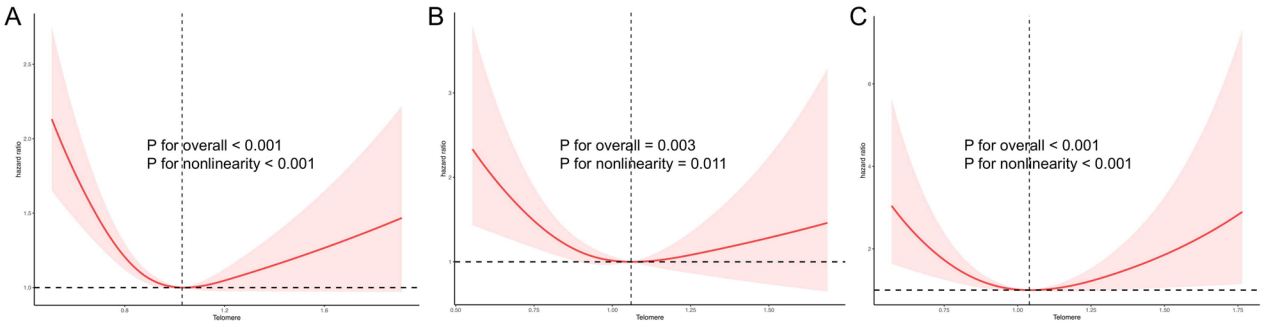

Figure 3. The RCS curves for the relationship between LTL with all-cause and cause-specific mortality. (A) All-cause mortality, (B) cardiovascular death, and (C) cancer-caused mortality. The RCS model was adjusted for age, sex, ethnicity, PIR smoker, alcohol user, hypertension, DM, BMI, Alb, TB, CRP, eGFR, Scr, uric acid, BUN, HDL-C, LDL-C, GGT, LYM, WBC, RBC, and Hb.

Subgroup	HR (95% CI)_in_T2	HR (95% CI)_in_T3	p.for.trend	p.for.interaction
All patients	**0.66 (0.54 – 0.80)**	**0.59 (0.47 – 0.73)**	**<0.001**	
Age(years)				**0.004**
<= 65	0.51 (0.32 – 0.80)	0.36 (0.23 – 0.56)	<0.001	
> 65	0.70 (0.56 – 0.86)	0.77 (0.63 – 0.93)	0.07	
Sex				**0.91**
Men	0.71 (0.57 – 0.88)	0.56 (0.40 – 0.78)	0.39	
Women	0.62 (0.46 – 0.84)	0.60 (0.42 – 0.86)	0.004	
Smoke				**0.07**
No	0.64 (0.52 – 0.78)	0.63 (0.52 – 0.78)	0.25	
Yes	0.74 (0.47 – 1.17)	0.45 (0.23 – 0.87)	0.01	
Hypertension				**0.003**
No	0.52 (0.32 – 0.86)	0.36 (0.22 – 0.59)	0.02	
Yes	0.69 (0.56 – 0.84)	0.66 (0.53 – 0.83)	<0.001	
DM				**0.74**
No	0.64 (0.51 – 0.79)	0.62 (0.47 – 0.81)	0.5	
Yes	0.70 (0.51 – 0.94)	0.60 (0.42 – 0.86)	0.01	

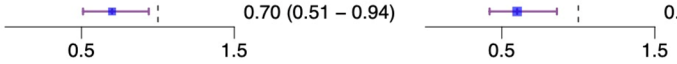

Figure 4. Forest plots for the relationship between LTL and all-cause mortality in different subgroups. Stratified analyses were adjusted for age, sex, ethnicity, PIR smoker, alcohol user, hypertension, DM, BMI, Alb, TB, CRP, eGFR, Scr, uric acid, BUN, HDL-C, LDL-C, GGT, LYM, WBC, RBC, and Hb. Data were adjusted for NHANES survey weights. T1: tertile 1; T2: tertile 2; T3: tertile 3; DM: diabetes mellitus; HR: hazard ratio; CI: confidence interval.

the inconsistency include the dissimilarity of age, ethnicity, or CKD severity. Future investigations should be performed to gain better insight into the role of LTL in predicting mortality among CKD patients.

To the best of our knowledge, this study is the first to describe the correlation between LTL and mortality risk due to cancer in CKD patients from an American cohort. Participants with a greater eGFR had a higher cancer incidence [46]. We observed that shorter LTL was associated with lower eGFR across all included participants. However, albuminuria was also found to be associated with LTL shortening. This finding suggests that, in the early stages of CKD, when eGFR is relatively preserved, LTL shortening may be more closely related to the presence of albuminuria rather than to the declined eGFR. We also found that patients with greater LTL had negative relation to cancer mortality regardless of age, sex, smoking status, alcohol consumption status, and history of DM and hypertension. LTL is a significant reference for doctors in choosing suitable prevention and treatment options to improve survival outcomes. Few previous studies have estimated the risk of cancer mortality in CKD patients. Higher cancer mortality was associated with lower eGFRs among patients whose eGFRs were lower than 60 mL/min/1.73 m^2 [24]. Moreover, the number of cancer-related deaths, especially myeloma and urologic cancers, has dramatically increased among patients with CKD [47]. Strategies are needed to prevent and control cancer-related mortality in participants with CKD. The factors that affect cancer mortality in CKD patients are complex. Patients with renal dysfunction are prevented from receiving nephrotoxic tumor therapy in the clinic [48]. On the other hand, many cancer trials excluded participants with abnormal renal function, which disrupted the use of cancer therapies in patients with CKD [49]. Further convincing investigations are needed to confirm the occurrence of cancer-related mortality in CKD patients. It is essential to enhance the management of CKD by applying strong strategies and our findings to clinical practice.

Next, we found that age and hypertension correlated with the dependency link between LTL and all kinds of mortality. Patients with shorter LTLs had worse survival among those younger than 65 years and those with hypertension. In general, LTL has the opposite correlation with

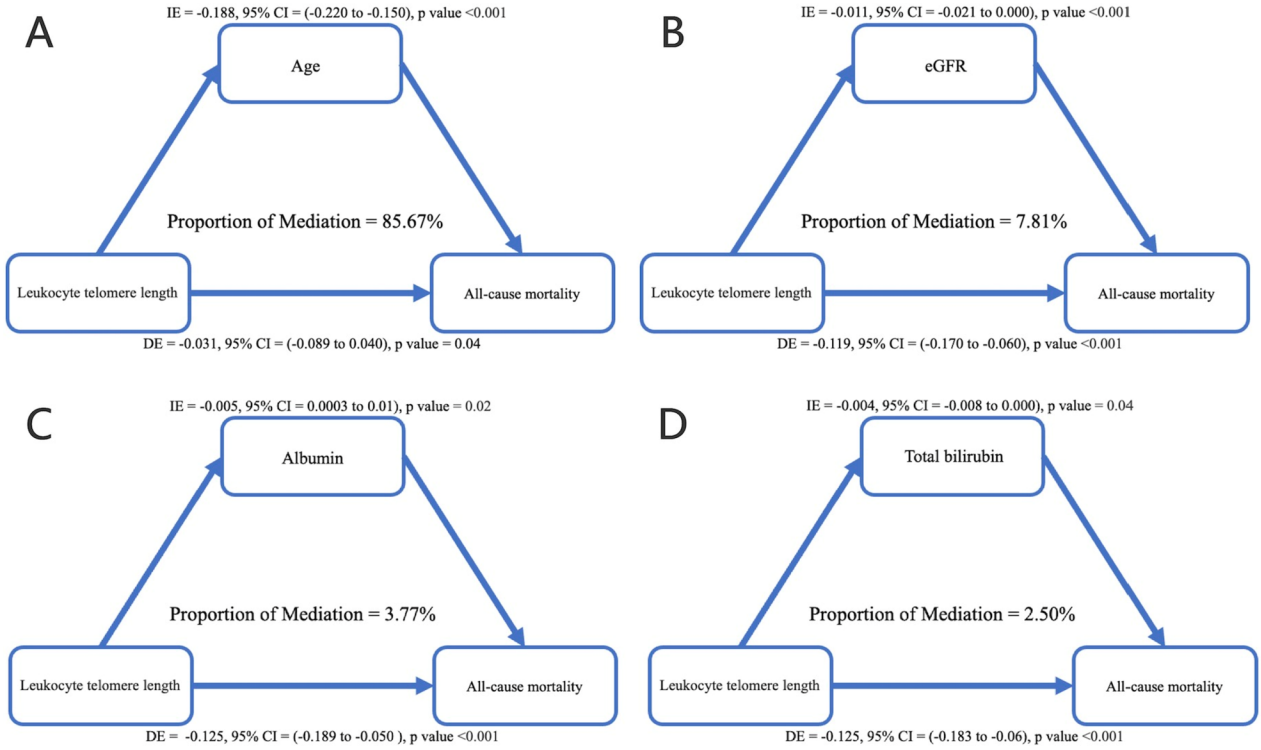

Figure 5. Factors mediated the relationship between LTL and all-cause mortality. The mediation analysis was adjusted for age, sex, ethnicity, PIR smoker, alcohol user, hypertension, DM, BMI, Alb, TB, CRP, eGFR, Scr, uric acid, BUN, HDL-C, LDL-C, GGT, LYM, WBC, RBC, and Hb. IE: indirect effects; DE: direct effects; eGFR: estimated glomerular filtration rate.

Table 3. The association between LTL and mortality after excluding individuals died within 2-year-follow-up.

	Model 1		Model 2		Model 3	
Character	HR (95% CI)	*p* Value	95% CI	*p* Value	HR (95% CI)	*p* Value
All-cause						
T1	–	–	–	–	–	–
T2	0.55 (0.43–0.69)***	<.001	0.69 (0.58–0.81)***	<.001	0.69 (0.59–0.82)***	<.001
T3	0.29 (0.23–0.38)***	<.001	0.60 (0.46–0.77)***	<.001	0.61 (0.50–0.75)***	<.001
CVD						
T1	–	–	–	–	–	–
T2	0.46 (0.32–0.68)***	<.001	0.55 (0.40–0.74)***	<.001	0.60 (0.43–0.83)	.002
T3	0.17 (0.11–0.27)***	<.001	0.44 (0.27–0.71)***	<.001	0.45 (0.31–0.66)***	<.001
Cancer						
T1	–	–	–	–	–	–
T2	0.35 (0.21–0.60)***	<.001	0.40 (0.25–0.63)***	<.001	0.48 (0.28–0.80)	.010
T3	0.12 (0.07–0.21)***	<.001	0.29 (0.16–0.52)***	<.001	0.32 (0.17–0.60)***	<.001

T1: tertile 1; T2: tertile 2; T3: tertile 3; CVD: cardiovascular disease; HR: hazard ratio; CI: confidence interval.
Data were adjusted for NHANES survey weights. Model 1 was unadjusted. Model 2 was modified for age, sex, ethnicity, PIR smoker, alcohol user, hypertension, DM, and BMI based on model 1. Model 3 was further adjusted for Alb, TB, CRP, eGFR, Scr, uric acid, BUN, HDL-C, LDL-C, GGT, LYM, WBC, RBC, and Hb.
***$p < .001$.

senescence [50,51]. The LTL gradually decreased with increasing age [52]. Other studies reported a correlation between abnormal LTL and senility [53]. Cell senescence results from LTL shortening, which impairs the regeneration and function of the kidney [54]. Moreover, we found a more obvious relationship between LTL and a lower risk of mortality in patients with hypertension than in those without hypertension. Increased blood pressure is regarded as a valid predictor in the early stage of renal dysfunction, where oxidative stress might affect this outcome [55,56]. The correlation between LTL and death was more distinct in patients with hypertension. Thus, LTL might be a useful predictor of prognosis among CKD patients with hypertension [57]. Moreover, we found that a history of smoking and DM were related to LTL and CVD-related death. A previous study reported that shorter LTL worsened CKD progression, especially in smokers and DM patients [17]; these patients were more likely to have increased oxidative stress. More surveys are necessary to elucidate whether LTL varies in different patients.

Age was the most important mediating factor in the association between LTL and all-cause mortality in our study. Therefore, research on the associations among LTL, aging and renal function is needed for the sake of improving renal function and lowering mortality, which might reduce health care costs for aging populations. As shown in the mediation analysis, the eGFR was also an important mediator of LTL-induced decreases in all-cause mortality. LTL related with decreased mortality via renal function. Oxidative stress leads to single-strand DNA destruction, which is pivotal for LTL shortening when DNA replicates [58,59]. Oxidative stress might play a key role in the outcomes of CKD patients with shorter LTL [60,61]. In accordance with previous studies, we further considered the levels of Alb, TB, and GGT as biomarkers of oxidative stress. Furthermore, Alb and TB also mediated the association, and the proportions of indirect effects were 3.77% and 2.50%, respectively. Our results support the idea that biomarkers of oxidative stress may be involved in the correlation between LTL and mortality. At present, most studies on the potential mechanism by which LTL regulates oxidative stress have focused on mitochondrial function. Telomerase is composed of telomerase reverse transcriptase (TERT) and a small RNA [62]. TERT is reportedly located in cellular mitochondria and is involved in the DNA damage response [63–65]. Shortening telomeres gives rise to oxidative stress in mitochondria by increasing the expression of p53 and decreasing PGC-1α expression, which is accompanied by the generation of reactive oxygen species (ROS) [66]. Moreover, TERT controls the balance of Ca^{2+} and mitochondria within the cell through the p53/PGC-1α pathway [67]. Redundant Ca^{2+} and damaged DNA in mitochondria lead to increased production of ROS and cellular senescence [68,69]. The findings concerning the connection of LTL with indicators of oxidative stress in survival are innovative and helpful for further studies about oxidative stress.

Compared with previous studies on LTL and mortality in the population, our study contributes to the body of knowledge by performing a comprehensive analysis of the relationships among LTL, age, oxidative stress, and renal function. We took relative covariates, including sociodemographic characteristics, markers of renal function and oxidative stress, into consideration to indicate the predictive value of LTL. The robustness of our findings was confirmed by sensitivity analyses. Nevertheless, further research is needed to discover the detailed connection between LTL and specific types of death in various individuals, such as patients with hypertension or DM. Inevitably, our study has several limitations. First, since the database from the NHANES is cross-sectional, we could not identify a rational causal association between LTL and mortality. More prospective studies are needed to verify causality in the future. Second, despite controlling for covariates, other potentially confounding factors were not considered. Third, missing data were filled by multiple imputation to maintain completeness, which might have led to inaccuracies during analysis. Further clinical investigations are warranted to substantiate this perspective. Finally, the indicators of oxidative stress selected in our study might not completely replace the level of oxidative stress in patients with CKD, and more experimental data are needed to validate our findings in the future. Overall, a better prognosis related to LTL is a complicated field of research that involves multiple molecular mechanisms. Further prospective studies assessing indicators of renal function as well as the relevance of oxidative stress to LTL and mortality are needed to explore the mechanisms linking these two conditions.

Conclusions

This study revealed that LTL was a protective factor for survival among patients with CKD and emphasized the mediating roles of oxidative stress and kidney function in clinical practice. The causal link needs further prospective investigations for validation to determine the risk of death and develop effective strategies for CKD prevention.

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Author contributions

JHY conceived and designed the study, acquired the data and drafted the manuscript; CJ analyzed the data; JHY and CJ contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content; JHY developed the software and provided technical support. LPX had the primary responsibility for final content.

Ethical approval

The database in our research was obtained from NHANES 1999–2002. The National Centre for Health Statistics Research Ethics Review Board (NCHS ERB) approved this program.

Consent form

All enrolled patients signed the informed consent in written form. And the process was censored and ratified by NCHS ERB.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The datasets generated and analyzed during the current study are available in NHANES and could be accessed at https://www.cdc.gov/nchs/nhanes/index.htm

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