

Plasma creatine kinase and all-cause mortality in patients on peritoneal dialysis: a multi-center retrospective study

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Abstract

Background: Higher plasma creatine kinase (CK) values are associated with the failure of antihypertensive treatment. However, an association between CK and all-cause mortality in peritoneal dialysis (PD) patients has received little attention.

Methods: In this retrospective multicenter study, 2224 incident PD patients with baseline CK values were enrolled from November 1, 2005, to February 28, 2017. All patients with oral statins were excluded and then were divided into four groups [Quartile 1 (<60 U/L), Quartile 2 (60-100 U/L), Quartile 3 (101-179 U/L), and Quartile 4 (>179 U/L)]. The primary endpoint was all-cause mortality. The association between plasma CK values and all-cause mortality was assessed with Cox regression and the Fine and Gray models.

Results: Of eligible 1382 patients, 298 (21.6%) patients died during a median 35-month (interquartile range=19-54 months) follow-up period. Patients in Quartile 4 were older ($P<0.001$), more likely to be male ($P<0.001$), had a higher prevalence of diabetes ($P=0.002$), and a history of cardiovascular disease ($P=0.005$), and higher values of Charlson comorbidity index ($P=0.031$). All-cause mortality incidence had a significant difference among the four Quartiles (Quartile 1, 16.2%; Quartile 2, 22.2%; Quartile 3, 23.8%; Quartile 4, 24.1%; $P=0.043$). Quartile 4 had a higher all-cause mortality compared to other groups (Log Rank=10.55, $P=0.015$). After adjusting for confounding factors, the highest CK quartile had a hazard ratio (HR) for all-cause mortality of 1.72 [95% confidence interval (CI) 1.31-3.26, $P=0.042$]. With kidney transplantation or hemodialysis as a competing risk, the Quartile 4 had an HR for all-cause mortality of 1.64 (95%CI 1.25-3.48, $P=0.046$), after adjusting for confounding factors.

Conclusions: Higher plasma CK levels at the commencement of PD may be a valuable biomarker for predicting the development of all-cause mortality in PD patients.

Background

High creatine kinase (CK), as a significant predictor for blood pressure (BP) and the failure of antihypertensive drugs, is associated with the failure of antihypertensive treatment in the general population [1]. Previous studies have shown that high CK activity promotes hypertension by enhancing vasoconstriction and renal sodium retention [2-4]. Additionally, previous studies show that plasma CK levels are associated with decreased inflammation in obesity, whereas higher inflammation is associated with higher obesity-related cardiovascular disease (CVD) [5-7]. Another study reported that plasma CK levels were inversely and independently associated with C-reactive protein in 454 overweight and obese individuals, supporting the anti-inflammatory effects of plasma CK levels [8]. Thus, plasma CK may have beneficial and detrimental effects on prognosis in the general population.

Among peritoneal dialysis (PD) patients, chronic inflammation is a well-recognized nontraditional risk factor that contributes to excessive mortality [9]. Therefore, plasma CK supporting the anti-inflammatory effects may also have a beneficial effect on the prognosis of PD patients. However, on the other hand,

high plasma CK levels promote hypertension through enhanced vascular contractility and renal sodium retention [2]. Thus, these findings suggested that plasma CK may also have beneficial and detrimental effects on clinical outcomes in PD patients. Therefore, it was difficult to speculate on the association between plasma CK levels and mortality in PD patients. The aim of this study was to evaluate the association between plasma CK levels and mortality in PD patients.

Methods

Study Population and Data Collection

We retrospectively conducted a multicenter cohort study of incident patients with PD from four PD centers from November 1, 2005, to February 28, 2017. Patients lacking plasma CK at baseline, with aged < 18 years, or with PD vintage < three months were excluded from this study. We excluded those using statins because statins may increase plasma CK levels. The study was consistent with the ethical principles of the Declaration of Helsinki and was approved by the Human Ethics Committee of each research center. Written informed consent was obtained from all participants.

Baseline demographic data included age, sex, diabetes, a history of CVD, hypertension, Charlson comorbidity index (CCI), and medication use [including calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), diuretics and β -blockers]. Clinical and biochemical data at the initiation of PD included body mass index (BMI), BP, hemoglobin, albumin, total cholesterol, triglycerides, aspartate aminotransferase (AST), alanine transaminase (ALT), serum uric acid, creatinine, high-sensitivity C-reactive protein (hs-CRP), serum sodium, calcium, phosphorus, and 24-hr urine output. The CK values at the initiation of PD were also collected under resting conditions. CVD was defined as coronary events, arrhythmias, congestive heart failure, cerebrovascular events, or peripheral vascular disease [10]. As one of the most commonly used comorbidity models, the comorbidity score was determined based on the CCI [11].

The primary endpoint was all-cause mortality, which was determined by the PD follow-up panels composed of PD primary nurses and professors. If death had two or more potential causes, we generally ascribed the death to the primary cause for hospitalization or the initial presenting condition. If a patient died within three months of transfer to hemodialysis therapy, he or she was not censored because the early mortality was considered to reflect health status during the period of failing PD treatment. All patients were followed up until the cessation of PD, death, or May 31, 2017. The censored data included switching to HD, kidney transplantation, moving to another center, loss to follow-up, or still at four PD centers with a follow-up duration of 8 years. All patients received continuous ambulatory PD treatment. Conventional PD solutions (Dianeal 1.5%, 2.5%, or 4.25% dextrose; Baxter Healthcare, Guangzhou, China), Y sets, and twin bag systems were used in all PD patients.

Statistical Analyses

Eligible patients were stratified into four groups: Quartile 1<60 U/L, Quartile 2=60-100 U/L, Quartile 3=101-179 U/L, and Quartile 4>179 U/L. Continuous variables were presented as mean \pm standard deviation or median and categorical variables as frequency and percentage. Comparisons of variables among groups were undergone using the Chi-squared test, one-way ANOVA, or the Kruskal-Wallis test. The correlations between plasma CK levels and baseline variables were assessed by correlation analysis. Survival times were estimated from Kaplan–Meier curves, and differences in survival probability among groups were assessed using a Log Rank test. The association between CK Quartiles and all-cause mortality was evaluated by the Cox regression model. Unadjusted associations (model 1) were first examined, followed by adjustments for age, sex, CCI, and the use of medication (model 2). Next, systolic and diastolic BP, hemoglobin, albumin, creatinine, sodium, calcium, phosphorus, and 24-hour urine output were added into model 2 (model 3).

Sensitivity Analyses

The Fine and Gray competing risk model was performed with the covariates included in the Cox regression model, and kidney transplantation or transfer to hemodialysis was considered as the competing event.

The results of the Cox analysis and the Fine and Gray method were presented as the hazard ratio (HR) and the 95% confidence interval (CI). A value of $P<0.05$ was considered statistically significant. Statistical analyses were performed using GraphPad software 8.0 (GraphPad Prism Software Inc., San Diego, California) and the R package (<https://www.r-project.org/>).

Results

Baseline Patient Characteristics

Of 2224 incident PD patients, 10 patients were younger than 18 years, 84 patients were on PD less than three months, 196 patients were using statins, and 552 patients lacked plasma CK levels at baseline were excluded, with 1382 patients eligible for the present analysis (Figure 1). Of study patients with 51.1 ± 14.8 years, 56.9% were male, 23.4% had diabetic, 16.4% had a history of CVD, and 71.9% had hypertension. In addition, 72.9% taken CCB, 31.6% taken ACEI/ARB, 8.2% taken diuretic, and 31.9% taken β -blocker.

Baseline CK levels ranged from 8 to 13585 U/L (median=100 U/L, interquartile range=60-179 U/L). The baseline variables stratified by Quartiles were shown in Table 1. Patients in Quartile 4 were older ($P<0.001$), more likely to be male ($P<0.001$), had a higher prevalence of diabetes ($P=0.002$), and a history of cardiovascular disease ($P=0.005$), and higher values of CCI ($P=0.031$).

Correlation analyses showed that plasma CK levels were positively correlated with age ($P=0.001$), systolic BP ($P=0.027$), diastolic BP ($P=0.033$), sodium ($P=0.002$) and phosphorus levels ($P=0.001$) and were negatively correlated with calcium levels ($P=0.025$). There was no collinearity between hs-CRP and albumin (standardized coefficients=-0.052).

Quartiles of CK and All-Cause Mortality

Of all patients with 35 months (19-54 months) of median follow-up period, 298 (21.6%) had died, 70 (5.1%) had received kidney transplantation, 193 (14.0%) had transferred to hemodialysis, 7 (0.5%) had transferred to other PD centers, and 32 (2.3%) had been lost to follow-up. The remaining 782 (56.6%) patients were still followed at these PD centers. Of the 298 deaths, 196 (65.8%) deaths were caused by CVD, 54 (18.1%) deaths by infectious disease, 49 (16.4%) deaths by other reasons, and 45 (15.1%) deaths by an unknown reason. There were significant differences on all-cause mortality in these groups (Quartile 1, 16.2%; Quartile 2, 22.2%; Quartile 3, 23.8; Quartile 4, 24.1%; $P=0.043$). Subgroup analyses found that similar trends were observed in males and those without diabetes ($P=0.038$ and $P=0.035$). At the end of 1, 3 and 5 years, the all-cause mortality was 9%, 19% and 27% in the Quartile 1, 13%, 22% and 29% in the Quartile 2; 15%, 27% and 36% in the Quartile 3; and 16%, 29% and 42% in the Quartile 4.

Kaplan–Meier estimates of all-cause mortality among different Quartiles were shown (Figure 2). Patients with higher CK Quartiles had a higher cumulative all-cause mortality compared to those lower Quartiles (Log Rank=11.13, $P=0.012$). Similar results were observed in the male and non-diabetic patients (Log Rank=9.63, $P=0.045$; Log Rank=12.61, $P=0.006$). Adjusted HR for all-cause mortality in different Quartiles was shown in Table 2. Quartile 4 was independently associated with all-cause mortality, even after adjusting for demographics, comorbid conditions, and laboratory variables (Quartile 1 as a reference, HR=1.72, 95% CI 1.31-3.26, $P=0.042$). Subgroups analyzed showed that the Quartile 4 had an independently higher risk of all-cause mortality in males (HR=1.44, 95%CI 1.13-2.49, $P=0.023$) and non-diabetes (HR=1.61, 95%CI 1.43-2.52, $P=0.019$), after adjusting for confounding factors.

Sensitivity Analyses

With renal transplantation or hemodialysis as a competing risk event, the Quartile 4 had an adjusted HR for all-cause mortality of 1.64 (95%CI 1.25-3.48, $P=0.046$, Table 2) compared to the Quartile 1, after adjusting for confounding factors. Figure 3 showed that with renal transplantation or hemodialysis as a competing risk event, the Quartile 4 had independently higher risk of all-cause mortality in male (HR=1.36, 95%CI 1.08-2.55, $P=0.029$) and non-diabetes (HR=1.53, 95%CI 1.40-2.60, $P=0.026$) group, after adjusting for confounding factors.

Discussion

In this multicenter retrospective study, we found that even after adjustment for baseline variables, higher plasma CK levels were incrementally associated with a higher risk of all-cause mortality in PD patients, especially in those male and non-diabetes PD patients.

Plasma CK tightly binds to ATP-utilizing enzymes, including Ca^{2+} -ATPase, myosin ATPase, and Na^+/K^+ -ATPase, to rapidly regenerate ATP from ADP, H^+ , and phosphocreatine [12]. Usually, the release of CK from tissues is proportional to the intracellular CK concentration, a physiological process that occurs without tissue damage, as summarized by Brewster [3]. Therefore, the plasma CK of healthy people at rest reflects

the tissue CK concentration [3, 4, 13]. However, as lymphatic flow increases with exercise, CK from the interstitial space may enter the circulation rather abruptly and be cleared by the liver in approximately three days [3]. An elevation of plasma CK levels is seen following acute myocardial infarction, rhabdomyolysis, intramuscular injections, and strenuous physical activity. A high tissue CK level is thought to result in a phenotype with greater vasoconstriction and enhanced sodium retention by greater ATP-buffering capacity of ATPases involved in ion transport and contractile responses [2, 3, 12, 14].

Previous studies found that relatively high CK is thought to enhance ATP-demanding processes, including resistance to arterial contractility and sodium retention, and to reduce ADP-dependent function in the general population [12, 15][12, 15]. Subsequently, in a randomized sample of a multiethnic population in Amsterdam, the Netherlands, CK proved to be an important independent predictor of BP levels and the failure of antihypertensive treatment [3]. This study found that after adjusting for age, gender, BMI, and ethnicity, CK was independently associated with BP and with systolic and diastolic BP, increasing by 8.0 and 4.7 mmHg/log CK, respectively. Since then, several other studies have reported that plasma CK levels are associated with the failure of antihypertensive drug treatment [4, 15][4, 15]. In addition, plasma CK has been associated with decreased inflammation in obesity, while inflammation is associated with obesity-related CVD [14]. Notably, plasma CK along with lean body mass is inversely and independently associated with hs-CRP in overweight and obese individuals, supporting the anti-inflammatory effects of CK. Thus, these findings suggest that CK may also have beneficial and detrimental effects on the prognosis of patients. Therefore, it is difficult to speculate on the association between CK and death in PD patients. To date, little is known about the association between plasma CK levels and all-cause mortality in PD patients. Our study showed that high plasma CK Quartiles were associated with higher risk of all-cause mortality in PD patients, independent of confounding factors, such as age, sex, CCI, CCB use, ACEIs/ARBs use, β -blocker use and diuretic use. Meanwhile, we found that the results from the competing risk model were consistent with the Cox regression models. Additionally, similar results were also observed in the male and those without diabetes. These findings suggested that monitoring plasma CK levels may be beneficial for improving the prognosis of PD patients, especially in the male and those without diabetes.

A possible explanation for the described association between total plasma CK levels and mortality was that plasma CK was associated with the failure of antihypertensive therapy, which has been linked to higher mortality [16]. There is increasing evidence that high plasma CK levels are thought to enhance ATP-demanding processes, including resistance to arterial contractility and sodium retention. In our study, higher plasma CK levels were associated with a higher risk of all-cause death. Our results showed that there was a significantly positive relationship between the levels of plasma CK and BP. It is well known that high BP is associated with high all-cause mortality [16, 17]. Although the lowest Quartile of CK (<60 U/L) was associated with a lower risk of all-cause death, the mean hemoglobin and albumin levels in the Quartile 1 were significantly lower than those in the Quartile 4. It is well known that lower hemoglobin and albumin, as markers of malnutrition, are associated with a higher risk of all-cause mortality [18]. Additionally, lower plasma CK may be considered a marker of malnutrition and relatively low muscle mass, which has been linked to a higher risk of all-cause mortality [17, 19]. Thus, these findings

suggested that the adverse effect of the failure of antihypertensive treatment of higher CK levels on all-cause mortality may be stronger than the protective effect of anti-inflammatory of higher CK levels on all-cause mortality, which may lead to increased all-cause mortality in the present study. Therefore, mechanisms of the effect of plasma CK on mortality should be investigated in future studies, and the management of plasma CK may improve the clinical prognosis of PD patients.

The strengths of this study are the multicenter nature of the study, a large number of patients, the ability to adjust for significant risk factors for all-cause mortality, and sensitive analysis of competing risk model. There are some limitations in the present study. First, due to the multicenter design of the cohort, there were some variations in the ascertainment and validation of the endpoint. However, it was a multicenter study; therefore, center-specific effects may be excluded. Second, the retrospective nature of the study allows us to establish associations but not causal relationships. As with all retrospective studies, a potential limitation is that the associations may be influenced by confounding by other risk factors. Because of the restriction of sample size, we did not adjust for all factors associated with higher mortality. Therefore, the effect of residual confounding cannot be eliminated completely. Due to the retrospective data, we are not capable of getting precise home BP data because of patient's bias. We will prospectively observe the longitudinal association between plasma CK levels and BP of these patients. Third, guidelines of dialysis do not regularly recommend lipid-regulating treatment of hyperlipidemia and CVD events in PD patients. Thus, even though PD patients developed CVD events, we usually do not prescribe statins for these patients. This was why patients with statins accounted for < 10% of total PD patients. Nonetheless, the findings are mainly applicable in statin naïve subjects. Future study should focus on the relationship between CK levels and statins in PD patients. Fourth, whether plasma CK can be cleared via PD remains unknown. Thus, whether the patients with higher CK had greater clearance needs that were not met by the CAPD remains unknown. We will further observe the association between dialysis dose and plasma CK levels. Lastly, the changes in variables and treatments overtime during the follow-up were not included.

Conclusions

In conclusion, we found an independent association between higher plasma CK levels at the commencement of PD and a higher risk of all-cause mortality in PD patients, especially in males and those without diabetes. These findings suggest that monitoring plasma CK levels may be beneficial for improving the prognosis of PD patients, and clinicians could use plasma CK as a valuable biomarker for mortality in PD patients.

Declarations

Ethics approval and consent to participate: The study was consistent with the ethical principles of the Declaration of Helsinki and was approved by the Human Ethics Committee of the Second Affiliated Hospital of Guangzhou Medical University, Zhujiang Hospital of Southern Medical University, Jiujiang No.

1 People's Hospital, Affiliated Sixth People's Hospital, Shanghai Jiao Tong University, and the First Affiliated Hospital of Nanchang University. Written informed consent was obtained from all participants.

Consent for Publication: All authors have approved the submitted version. All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Availability of data and material: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: YQ W, contributions to the conception, interpretation of data, and drafted the work; FF P, the acquisition, analysis and interpretation of data; XR F, the acquisition, analysis and interpretation of data; NS W, contributions to the conception and design of the work; XJ Z, contributions to the conception and design of the work; XF W, contributions to the conception, design of the work, and revised it. All authors have read and approved the manuscript.

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Abbreviations

CK, creatine kinase; CVD, cardiovascular disease, CCI, Charlson comorbidity index; CCB, calcium channel blocker; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index, ALT, alanine transaminase, AST, aspartate aminotransferase; hs-CRP, high-sensitivity C-reactive protein.

References

1. Brewster LM, Karamat FA, van Montfrans GA: **Creatine Kinase and Blood Pressure: A Systematic Review.** *Med Sci (Basel)* 2019, **7**(4).
2. Brewster LM, Clark JF, van Montfrans GA: **Is greater tissue activity of creatine kinase the genetic factor increasing hypertension risk in black people of sub-Saharan African descent?** *J Hypertens* 2000, **18**(11):1537-1544.
3. Brewster LM, Mairuhu G, Bindraban NR, Koopmans RP, Clark JF, van Montfrans GA: **Creatine kinase activity is associated with blood pressure.** *Circulation* 2006, **114**(19):2034-2039.
4. Oudman I, Kewalbansingh PV, van Valkengoed I, Zwinderman AH, Clark JF, van Montfrans GA, Brewster LM: **Creatine kinase is associated with failure of hypertension treatment.** *J Hypertens* 2013, **31**(5):1025-1031.

5. Ding D, Wang M, Su D, Hong C, Li X, Yang Y, Zhang Y, Hu G, Ling W: **Body Mass Index, High-Sensitivity C-Reactive Protein and Mortality in Chinese with Coronary Artery Disease.** *PLoS One* 2015, **10**(8):e0135713.
6. Dutra MT, Avelar BP, Souza VC, Bottaro M, Oliveira RJ, Nobrega OT, Moreno Lima R: **Relationship between sarcopenic obesity-related phenotypes and inflammatory markers in postmenopausal women.** *Clin Physiol Funct Imaging* 2017, **37**(2):205-210.
7. Tajra V, Tibana RA, Vieira DC, de Farias DL, Teixeira TG, Funghetto SS, Silva AO, de Sousa NM, Willardson J, Karnikowski MG *et al.*: **Identification of high responders for interleukin-6 and creatine kinase following acute eccentric resistance exercise in elderly obese women.** *J Sci Med Sport* 2014, **17**(6):662-666.
8. Bekkelund SI, Jorde R: **Lean body mass and creatine kinase are associated with reduced inflammation in obesity.** *Eur J Clin Invest* 2017, **47**(11):803-811.
9. Li PK, Ng JK, McIntyre CW: **Inflammation and Peritoneal Dialysis.** *Semin Nephrol* 2017, **37**(1):54-65.
10. Bahrami H, Bluemke DA, Kronmal R, Bertoni AG, Lloyd-Jones DM, Shahar E, Szklo M, Lima JA: **Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study.** *J Am Coll Cardiol* 2008, **51**(18):1775-1783.
11. Charlson ME, Pompei P, Ales KL, MacKenzie CR: **A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.** *J Chronic Dis* 1987, **40**(5):373-383.
12. Brewster LM: **Creatine kinase, energy reserve, and hypertension: from bench to bedside.** *Ann Transl Med* 2018, **6**(15):292.
13. Brewster LM, Coronel CM, Sluiter W, Clark JF, van Montfrans GA: **Ethnic differences in tissue creatine kinase activity: an observational study.** *PLoS One* 2012, **7**(3):e32471.
14. Taherzadeh Z, Karamat FA, Ankum WM, Clark JF, van Montfrans GA, van Bavel E, Brewster LM: **The Effect of Creatine Kinase Inhibition on Contractile Properties of Human Resistance Arteries.** *Am J Hypertens* 2016, **29**(2):170-177.
15. Johnsen SH, Lilleng H, Wilsgaard T, Bekkelund SI: **Creatine kinase activity and blood pressure in a normal population: the Tromso study.** *J Hypertens* 2011, **29**(1):36-42.
16. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW *et al.*: **2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.** *Circulation* 2019, **140**(11):e596-e646.
17. Kaczmarek KR, Sozio SM, Chen J, Sang Y, Shafi T: **Resistant hypertension and cardiovascular disease mortality in the US: results from the National Health and Nutrition Examination Survey (NHANES).** *BMC Nephrol* 2019, **20**(1):138.
18. Lopez-Gomez JJ, Delgado-Garcia E, Coto-Garcia C, Torres-Torres B, Gomez-Hoyos E, Serrano-Valles C, Castro-Lozano A, Arenillas-Lara JF, de Luis-Roman DA: **Influence of Hyperglycemia Associated with Enteral Nutrition on Mortality in Patients with Stroke.** *Nutrients* 2019, **11**(5).

19. Nakayama A, Canales C, Yeh DD, Belcher D, McCarthy CM, Quraishi SA: **Patient- and Nutrition-Derived Outcome Risk Assessment Score as a Predictor of Mortality in Critically Ill Surgical Patients: A Retrospective, Single-Center Observational Study.** *Nutr Clin Pract* 2019, **34**(3):400-405.

Tables

Table 1. Baseline characteristics stratified by quartiles of baseline plasma CK levels

Variables	Quartile 1 (n=341)	Quartile 2 (n=345)	Quartile 3 (n=349)	Quartile 4 (n=347)	P value
Age (years)	49.4±15.1	50.4±14.3	50.8±14.3	54.0±15.3	<0.001
Male (%)	128 (37.5)	191 (55.4)	219 (62.8)	248 (71.5)	<0.001
Diabetes (%)	74 (21.7)	61 (17.7)	85 (24.4)	103 (29.7)	0.002
A history of CVD (%)	39 (11.5)	60 (17.4)	53 (15.2)	74 (21.4)	0.005
Hypertension (%)	274 (72.4)	250 (72.5)	247 (70.8)	250 (72.0)	0.955
CCI	4.51±1.37	4.37±1.34	4.56±1.53	4.69±1.57	0.031
CCB use (%)	231 (67.7)	257 (74.5)	259 (74.2)	260 (74.9)	0.109
ACEI/ARB use (%)	96 (28.2)	112 (32.5)	116 (33.2)	113 (32.6)	0.462
Diuretic use (%)	24 (7.0)	23 (6.7)	36 (10.3)	31 (8.9)	0.263
β-Blocker use (%)	118 (34.6)	116 (33.6)	118 (33.8)	89 (25.6)	0.038
BMI (kg/m ²)	21.8±3.4	22.2±3.2	22.1±3.2	22.6±3.1	0.013
Systolic BP (mmHg)	147±26	149±26	148±26	152±25	0.108
Diastolic BP (mmHg)	85±14	87±15	87±16	89±17	0.025
Hemoglobin (g/dl)	7.83±1.66	8.57±1.79	8.40±1.72	8.55±1.83	<0.001
Albumin (g/dl)	3.39±0.55	3.50±0.52	3.44±0.55	3.42±0.54	0.042
Cholesterol (mg/dl)	165±47	163±44	166±44	165±48	0.801
Triglycerides (mg/dl)	104 (74-150)	120 (83-173)	115 (82-155)	133 (91-200)	<0.001
ALT (u/l)	10 (6-16)	11 (7-17)	12 (8-18)	16 (9-26)	<0.001
AST (u/l)	16 (12-22)	16 (13-22)	17 (13-22)	20 (16-27)	<0.001

Uric acid (mg/dl)	7.19±2.24	7.57±2.24	7.65±2.02	7.38±2.03	0.052
Creatinine (µmol/L)	686±264	783±310	777±283	853±354	<0.001
hs-CRP (mg/dl)	20.5 (8.8- 36.7)	21.5 (5.2- 39.6)	18.8 (5.9- 37.9)	23.8 (8.9- 50.8)	0.154
Sodium (mg/dl)	319.0±10.2	320.9±8.9	321.5±8.3	323.3±7.4	<0.001
Calcium (mg/dl)	8.22±0.84	8.10±0.92	7.94±0.92	7.33±1.04	<0.001
Phosphorus (mg/dl)	6.81±2.08	7.21±2.44	7.49±2.36	7.74±2.24	<0.001
24-hr urine output (ml)	900 (500- 1200)	800 (465- 1200)	700 (350- 1100)	700 (500- 1100)	0.001

CK, creatine kinase; CVD, cardiovascular disease, CCI, Charlson comorbidity index; CCB, calcium channel blocker; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index, ALT, alanine transaminase, AST, aspartate aminotransferase; hs-CRP, high-sensitivity C-reactive protein.

Table 2. Adjusted hazards ratio for all-cause mortality in different CK quartiles.

		Model 1		Model 2		Model 3	
Plasma CK		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Cox	regression						
	model						
Quartile 1				reference			
Quartile 2		1.69 (1.23- 2.84)	0.003	1.68 (1.29- 2.96)	0.025	1.59 (1.22- 2.98)	0.032
Quartile 3		1.97 (1.24- 2.88)	0.005	1.83 (1.18- 2.86)	0.028	1.70 (1.13- 3.27)	0.038
Quartile 4		2.17 (1.31- 2.95)	0.023	1.96 (1.35- 2.94)	0.031	1.72 (1.31- 3.26)	0.042
Competing	risk						
	model*						
Quartile 1				reference			
Quartile 2		1.37 (1.21- 2.86)	0.007	1.63 (1.25- 2.99)	0.029	1.50 (1.17- 3.20)	0.034
Quartile 3		1.93 (1.20- 2.93)	0.015	1.79 (1.15- 2.96)	0.031	1.62 (1.09- 3.36)	0.040
Quartile 4		2.11 (1.30- 2.99)	0.026	1.92 (1.31- 2.98)	0.034	1.64 (1.25- 3.48)	0.046

*kidney transplantation or transfer to hemodialysis as a competing risk. Model 1: unadjusted. Model 2: adjusted for age, sex, CCI, and use of medication. Model 3: model 2 adjusted for systolic and diastolic BP, hemoglobin, albumin, creatinine, sodium, calcium, phosphorus and 24-hr urine output.

CK, creatine kinase; CCI, Charlson comorbidity index.

Figures

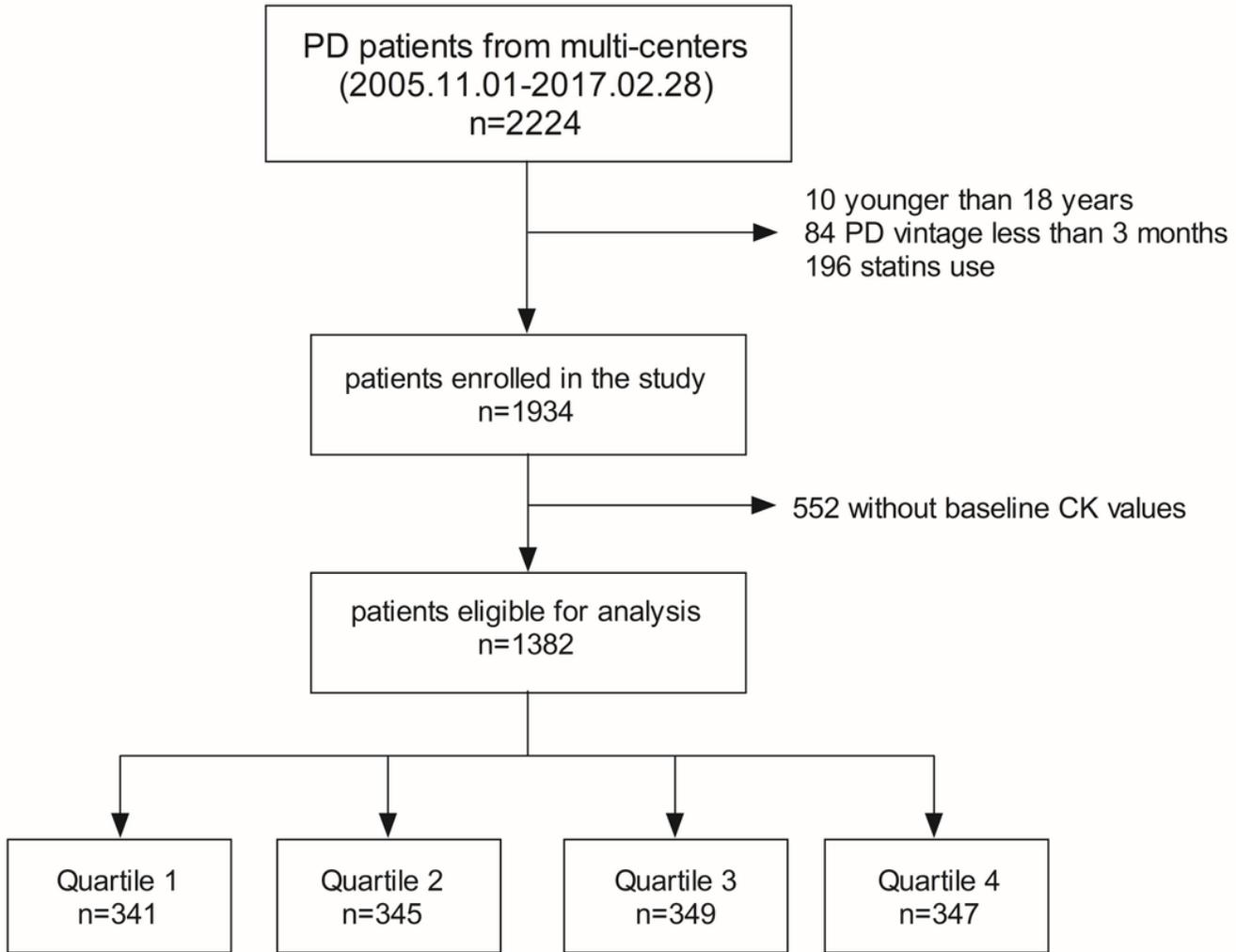


Figure 1

The flow chart showed how patients were selected for the present study. CK, creatine kinase.

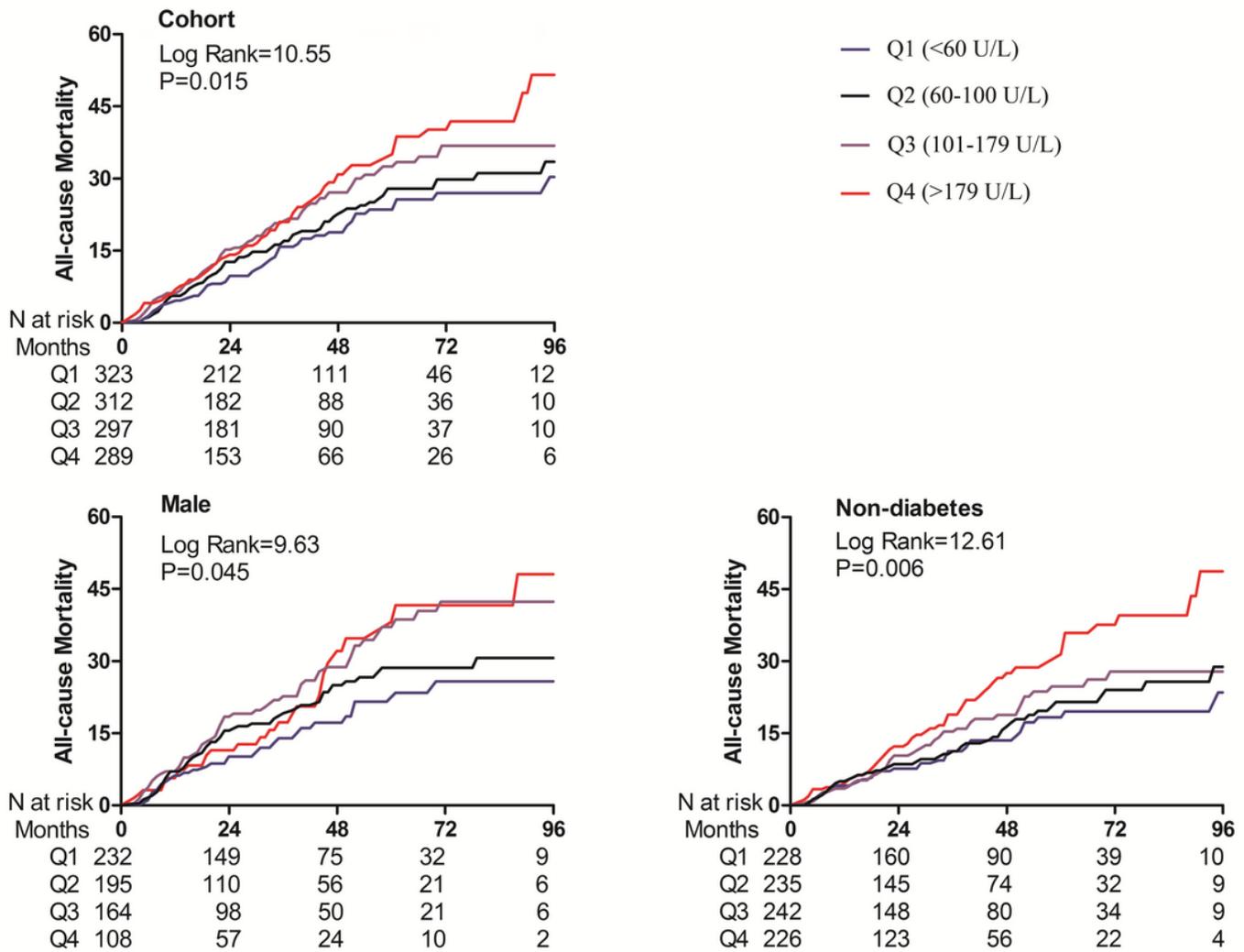


Figure 2

Adjusted hazards ratio for all-cause mortality. Hazard ratios for Quartile 4 relative to Quartile 1 (adjusted in multivariable models). CVD, cardiovascular disease.

Quartile 4 vs. Quartile 1 (as a reference)

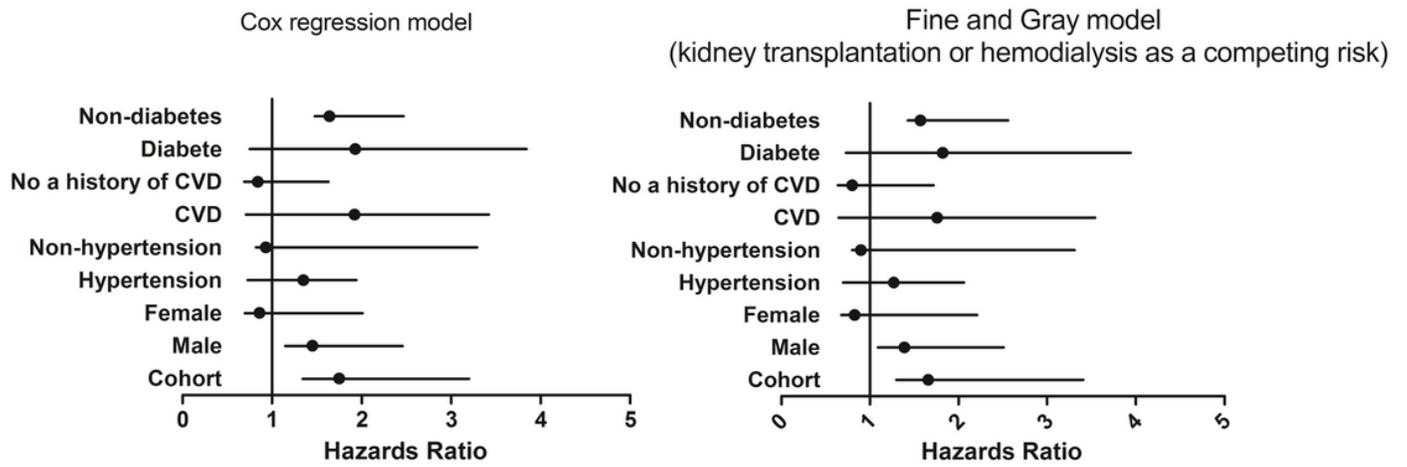


Figure 3

Cumulative all-cause mortality incidence for patients with different CK Quartiles. CK, creatine kinase.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplementarymaterials.docx](#)