Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Am J Kidney Dis. Author manuscript; available in PMC 2014 October 01.

Published in final edited form as:

Am J Kidney Dis. 2013 October ; 62(4): 703–710. doi:10.1053/j.ajkd.2013.04.012.

Prognostic Importance of Serum Alkaline Phosphatase in CKD Stages 3–4 in a Clinical Population

Jonathan J. Taliercio, DO[1], **Jesse D. Schold, PhD**[1,2], **James F. Simon, MD**[1], **Susana Arrigain, MA**[2], **Anne Tang, MS**[2], **Georges Saab, MD**[3], **Joseph V. Nally Jr, MD**[1,4], and **Sankar D. Navaneethan, MD, MPH**[1,4]

[1]Department of Nephrology and Hypertension, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH

[2]Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH

[3]Nephrology, Metro Health Medical Center, Cleveland, OH

[4]Cleveland Clinic Lerner College of Medicine of CWRU, Cleveland Clinic, Cleveland, OH

Abstract

Background—Elevated total serum alkaline phosphatase (ALP) levels have been associated with mortality in the general population and in dialysis patients.

Study Design—Retrospective cohort study.

Setting & Participants—28,678 patients with chronic kidney disease (CKD) stages 3 and 4 (estimated glomerular filtration rate [eGFR], 15–59 ml/min/1.73 m^2) were identified using the Cleveland Clinic Chronic Kidney Disease Registry. CKD was defined as two eGFR values <60 ml/min/1.73 m^2 drawn >90 days apart using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.

Predictor—ALP levels measured using the calorimetric assay was examined as quartiles (quartile 1, <66 U/L; Q2, 66–81 U/L; Q3, 82–101 U/L; and Q4, ≥102 U/L) and as a continuous measure.

Outcomes & Measurements—All-cause mortality and ESRD were ascertained using the Social Security Death Index and US Renal Data System.

© 2013 The National Kidney Foundation, Inc. Published by Elsevier Inc. All rights reserved.

Correspondence: Sankar D. Navaneethan, MD, MPH, Department of Nephrology and Hypertension, Glickman Urological and Kidney Institute, 9500 Euclid Avenue- Q7, Cleveland Clinic, Cleveland, Ohio-44195. Ph: 216 636 9230, Fax: 216 444 9378, navanes@ccf.org.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

The results of this study were presented as an abstract at the American Society of Nephrology annual meeting held November 2, 2012, in San Diego, CA.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Results—After a median follow up of 2.2 years, 588 patients progressed to ESRD and 4,755 died. There was a graded increase in the risk for mortality with higher ALP quartiles (Q2, Q3, Q4) when compared to the reference quartile (Q1) after adjusting for demographics, comorbid conditions, use of relevant medications and liver function tests. The highest quartile of ALP was associated with a hazard ratio for ESRD of 1.38 (95% CI, 1.09–1.76). Each 1-standard deviation (42.7 U/L) higher ALP level was associated with 15% (95% CI, 1.09–1.22) and 16% (95% CI, 1.14–1.18) increased risk of ESRD and mortality respectively.

Limitations—Single center observational study, lack complete data including PTH for all study participants and attrition bias.

Conclusions—Higher serum ALP levels in CKD stages 3–4 were independently associated with all-cause mortality and ESRD.

Keywords

alkaline phosphatase; end-stage renal disease; mortality; chronic kidney disease

Elevated serum alkaline phosphatase (ALP) contributes to the development and progression of vascular calcification[1,2]. Studies conducted in general population have shown independent associations between ALP and increased risk of cardiovascular events, hospitalization and death[3, 4]. Patients with CKD have higher ALP due to disturbances in the bone mineral disease which may contribute to the higher cardiovascular burden seen in this population. Previous studies have reported that an elevated ALP is associated with increased risk of coronary artery calcification and mortality in maintenance hemodialysis patients[5–7]. Recent studies have shown that in selective non-dialysis dependent CKD populations such as African Americans and males, higher ALP levels are associated with increased risk for all-cause mortality[8, 9].

The recently published Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that ALP be measured annually in patients with CKD stages 4 and 5 as an adjunct test when monitoring medical therapy or to assess for active bone turnover in the presence of secondary hyperparathyroidism[10]. While the previous studies examined the associations of ALP with mortality, its relationship with progression of kidney disease is unclear. We hypothesized that higher ALP levels are independently associated with an increased risk for ESRD and death in those with CKD stages 3 and 4 even after accounting for competing risks in this population. Therefore, we evaluated the relationship between ALP and ESRD and all-cause mortality in a large, diverse population withCKD stages 3–4 followed in our health care system.

Methods

Study Population

We conducted an analysis using our pre-existing electronic health record (EHR)-based CKD registry. The development and validation of this registry at Cleveland Clinic have been described in detail elsewhere[11]. Patients who met the following criteria between January 1, 2005 and September 15, 2009 were included in the study population: 1) had at least one

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

face-to-face outpatient encounter with a Cleveland Clinic health care provider, 2) had two eGFR values <60 ml/min/1.73 m^2 (using the CKD Epidemiology Collaboration [CKD-EPI] creatinine equation) more than 90 days apart and 3) had ALP measured between the first and second eGFR <60 ml/min/1.73 m^2 indicating CKD as an outpatient using a standard assay in our health system[12]. Patients aged <18 years old, who had eGFR <15 ml/min/1.73 m^2, and those who were diagnosed with ESRD needing dialysis or kidney transplantation prior to CKD diagnosis were excluded.

Definitions and Outcome Measures

Kidney function—We applied the 2009 CKD-EPI creatinine equation to patients who had two outpatient serum creatinine levels between January 1, 2005 and September 15, 2009 in our health system to calculate eGFR. All creatinine measurements were performed by the modified kinetic Jaffe reaction, using a Hitachi 747-200 Chemistry Analyzer (1996 to 2001) or a Hitachi D 2400 Modular Chemistry Analyzer thereafter (Roche Diagnostics, Indianapolis, IN) in our laboratory. All serum creatinine assays were standardized to isotope-dilution mass spectrometry (IDMS). CKD was defined according to the CKD-EPI equation-determined eGFR: CKD stage 3, eGFR 30–59 ml/min/1.73 m^2; CKD stage 4, eGFR 15–29 ml/min/1.73 m^2. We further categorized stage 3 into CKD stage 3a (eGFR 45–59 ml/min/1.73 m^2) and stage 3b (eGFR 30–44 ml/min/1.73 m^2). To be comprehensive and reflect clinical practice, patients who had urine dipstick measurements, urine albumin-creatinine ratio, urine protein-creatinine ratio and 24 hour urine studies were included to assess whether they had proteinuria. The following cut-offs were considered in determining whether someone had proteinuria: presence of ≥1+ proteinuria in dipstick studies, >30 mg/g in those who had urine albumin-creatinine ratio and urine protein-creatinine ratio studies and >30 mg proteinuria in 24 hour studies. Urine dipstick studies were performed using Multistix reagent strips (Siemens). Urine albumin was measured by immunoturbidimetric assay with antigen excess check on the Roche Modular platform in our laboratory. Urine creatinine was measured using a multistep enzymatic procedure that produces a quinone imine chromogen on the Roche Modular platform.

Serum alkaline phosphatase—ALP was measured using a colorimetric assay in accordance with a standardized method (Roche Modular Analyzer). Only outpatient laboratory measures were included in this analysis. For each patient, ALP level measured between the first and second eGFR <60 ml/min/1.73 m^2 was used for the analysis. When multiple measures per patient were available, the one closest to second eGFR <60 ml/min/1.73 m^2 was selected.

Comorbid conditions and laboratory parameters—Demographic details were extracted from the EHR. Diabetes mellitus, hypertension, coronary artery disease, and other comorbid conditions were defined using pre-specified criteria and validated in a previous publication. ALP levels and other relevant outpatient laboratory details were obtained from our electronic laboratory records.

Outcome measures—The primary outcomes of interest, all-cause mortality and ESRD, were ascertained from our EHR and linkage of our CKD registry with the Social Security

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Death Index and US Renal Data Services (USRDS). Patients were followed up from their date of inclusion in the registry (date of second qualifying eGFR) until September 15, 2009.

Statistical Analysis

CKD patients with and without ALP were compared on their baseline characteristics using Chi-square tests for categorical variables and t-tests or Wilcoxon rank-sum tests for continuous variables. CKD patients with measured outpatient ALP values were classified into quartiles: quartile 1, <66 U/L; Q2, 66–81 U/L; Q3, 82–101 U/L; and Q4, ≥102 U/L. Associations of the baseline characteristics and these four groups were assessed using Cochran-Armitage trend test for binary variables, Chi-square test for categorical variables with 3 levels or more, and ANOVA tests or Kruskal-Wallis tests for continuous variables.

To evaluate whether survival and ESRD among persons with CKD stages 3–4 was associated with ALP, we used Kaplan-Meier plots and log-rank tests with second eGFR <60 ml/min/1.73 m^2 as the time of origin. Progression to ESRD and pre-ESRD death are competing events; therefore we fitted cumulative incidence functions that adjust for competing risks and compared these results to the traditional cause-specific analysis. In addition, a separate analysis that included all deaths (both before and after ESRD) was also conducted. We used Cox proportional hazards models to assess the association between ALP and mortality and ESRD while adjusting for other covariates. Covariates were chosen *a priori* based on factors previously shown or thought to be related to both ALP and mortality. These include age, gender, race, body mass index (BMI), eGFR, diabetes, hypertension, hyperlipidemia, use of statins, malignancy, coronary artery disease, cerebrovascular disease, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, heart failure, smoking, serum albumin, hemoglobin, bicarbonate, aspartate aminotransferase (AST), alanine transaminase (ALT), bilirubin and calcium. The missing covariate data among the 28,678 patients is as follows: BMI, 1167 (4%); smoking, 3731 (13%); bicarbonate, 51 (<0.5%); AST, 284 (1%); ALT, 224 (0.8%); bilirubin, 301 (1%); calcium, 52 (<0.5%); serum albumin, 296 (1%); and hemoglobin, 2063 (7%). We used multiple imputation (SAS “PROC MI”) with the Markov Chain Monte Carlo method and a single chain to impute 5 datasets with complete covariate data. All Cox models were performed on each of the 5 imputed datasets and the parameter estimates and standard errors were combined using SAS “MIANALYZE”.

The relationship between ALP and each outcome was evaluated 2 ways: with continuous ALP, and with ALP quartiles. We tested the interaction between eGFR and continuous ALP and stratified the associations by CKD stages. We did not adjust for proteinuria or phosphorus in our main models because we only had data in approximately 50% and 20% of the sample, respectively. However, we did sensitivity analyses fitting cox models with continuous ALP as described above and adjusting for proteinuria and serum phosphorus in separate analyses. We also did an additional sensitivity analysis that included only patients with ALP within the normal range (<149 U/L). All sensitivity analyses were also done on the 5 imputed datasets and the results combined using MIANALYZE.

All data analyses were conducted using Unix SAS version 9.2 (SAS Institute Inc, Cary, NC) and R statistical software version 2.12.2 (R Foundation for Statistical Computing, Vienna,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Austria). The “cmprsk” package was used for competing risk analysis. The CKD registry and this study were approved by the Cleveland Clinic Institutional Review Board.

Results

Baseline Patient Characteristics

We included 28,678 patients who had an ALP level between the first and second eGFR <60 ml/min/1.73 m^2 (Figure 1). Mean age of the study population was 72 ±12 (standard deviation) years with 54% being females and 12% African Americans. The majority of patients were either overweight (35%) or obese (35%). There was a statistically significant difference among the groups (based on the quartiles of ALP) in the prevalence of hypertension, congestive heart failure, use of angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers, use of statins, hemoglobin, hyperlipidemia, and bicarbonate levels (p<0.001) (Table 1). Liver function tests such as AST, ALT, serum albumin and bilirubin were also significantly different, but the mean values for the entire cohort were all within the normal laboratory values. There was a progressive increase in PTH values from the lowest to highest quartiles of ALP, but a large number of patients were missing PTH results (p<0.001). There was no significant difference between the groups in the prevalence of coronary artery disease, and cerebrovascular disease (Table 1).

The proportion of missing data was similar across quartiles for all variables with missing data except for the following variables: hemoglobin, 8%, 8%, 7%, and 5%; proteinuria, 50%, 50%, 52%, and 51%; phosphorus, 82%, 83%, 82%, and 74%; and iPTH, 90%, 91%, 90%, and 87% all for quartiles 1–4, respectively. Patients with and without ALP levels measured were significantly different on all variables compared except for hemoglobin, though some of the absolute differences were small (Table 1).

ALP, ESRD, and All-Cause Mortality

After a median follow up of 2.2 years, 588 patients developed ESRD, while 4,755 died before reaching ESRD. There were 191 patients who developed ESRD and later died. Both the Kaplan-Meier and competing risk analyses showed a significant difference in overall mortality and ESRD among those with different ALP levels (p<0.001, Figure 2) and the results were similar in both analytical approaches.

ALP Quartiles

After adjusting for demographics, comorbid conditions, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, use of statins, serum albumin, hemoglobin, bicarbonate, eGFR, AST, ALT, bilirubin and calcium, there was a graded increase in the hazard for death in each quartile when compared to the reference (Table 2). Results were similar for overall death (pre and post-ESRD, data not shown). Even though there was a graded increase in the risk for ESRD with higher quartiles of ALP, the associations between ALP and ESRD was statistically significant only for those with ALP >102 U/L (quartile 4) (Table 2).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Continuous Variable Analysis

The associations between ALP and death and ALP and ESRD were similar when examined as a continuous variable (Table 2). In the multivariate adjusted analysis, each standard deviation higher ALP (42.7 U/L) was associated with a 16% increased hazard for death and 15% increased hazard for ESRD (Table 2). Results were similar for overall death (pre and post-ESRD, data not shown). We found a significant interaction between eGFR and ALP on mortality, and when stratifying based on CKD stage, we found that the hazardous effect of ALP was stronger at higher levels of eGFR (Figure 3). We did not find a significant interaction between eGFR and ALP on ESRD.

Sensitivity Analysis

When the analysis was restricted to those who had ALP levels within the normal range (<149 U/L), similar results were noted (data not shown). In a subgroup analysis that included patients who had serum phosphorus data (n=5667), we found that while adjusting for serum phosphorus, each 1-standard deviation higher ALP (42.7 U/L) was associated with a 10% increased hazard for mortality (95% confidence interval [CI], 1.06–1.14), and a non-significant 9% increased risk for ESRD (95%CI, 0.99–1.19). In a subgroup analysis that included patients with at least one urinary protein measure (n=14,116), and after adjusting for all covariates plus proteinuria, each standard deviation higher ALP (42.7 U/L) was associated with a 16% increased hazard for mortality (95%CI, 1.12–1.19), and 17% increased hazard (95%CI, 1.07–1.26) for ESRD.

Discussion

Historically, ALP has only been considered a surrogate of bone metabolism in patients with CKD and ESRD. This study, along with other recently published studies, argues against this widely held perception[6, 7, 9]. In a diverse population with CKD stages 3 and 4, we noted a graded increase in the risk for the composite outcome of all-cause mortality and ESRD even after adjusting for relevant confounding variables. Similar results were obtained when the analysis was restricted to those who had ALP levels within the normal ranges (< 149 U/L) highlighting that even high-normal values of ALP might be associated with risk for adverse outcomes. To our knowledge, this is the first study to demonstrate elevated ALP increases the risk of ESRD and confirms the associations between elevated ALP levels and mortality in a more heterogeneous population of patients with CKD stages 3–4 than has been reported previously.

Elevated ALP levels have been associated with mortality in the general population and in those with ESRD[3, 4, 6, 7]. Tonelli et al. reported a graded, independent association (27% increased risk) between higher levels of ALP and mortality in the general population using National Health and Nutrition Examination Survey (NHANES) data[4]. Abramowitz et al. reported that among patients with eGFR ≥ 60 ml/min/1.73 m^2, ALP >104 U/L was associated with 65% higher risk for death[3]. The ALP levels which portrayed an increased risk of death in both these studies were within the normal references ranges, similar to our study findings pointing out the importance of monitoring those with high-normal ALP values. Analysis from the Dialysis Outcomes & Practice Patterns Study (DOPPS) showed a

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

25% increased risk of all-cause mortality and 38% increased risk of hospitalization in patients with mild to markedly elevated ALP compared to normal controls[7].

Few studies have examined the associations between ALP and mortality in a non-dialysis dependent CKD population. Beddhu et al. reported that doubling of ALP was associated with a 55% increase rate in all-cause mortality in the African American Study of Kidney Disease and Hypertension (AASK) cohort[8]. There was no association noted between ALP and the composite of death, dialysis, or GFR event. Another study including a veteran population with CKD stages 1–5 reported a 17% risk of death for every 50 U/L increase in ALP. After multivariate adjustment, the higher (>105 U/L) and lower (<66 U/L) quartiles were associated with all-cause mortality and a composite of pre-dialysis mortality and ESRD[9]. Our study confirms the associations of ALP with mortality, and differs from the aforementioned studies because it samples a more diverse population, and reveals the independent associations between ALP and ESRD.

ALP is derived from various tissue origins, but is mostly concentrated in the liver, biliary ducts, bone, and placenta. Tissue-nonspecific alkaline phosphatase inactivates pyrophosphate, an endogenous inhibitor of hydroxyapatite formation, resulting in medial arterial vascular calcification[13]. Under conditions such as hypertension, aging, diabetes and CKD, vascular cells undergo osteoblastic differentiation, and express several bone associated proteins, which includes alkaline phosphatase. Subsequently, this leads to mineralization of the endothelium, arterial stiffening and vascular calcification thereby contributing to the cardiovascular disease and mortality in CKD[1, 14]. ALP has been shown to be associated with arterial calcification in the coronary, carotid, and aorta, and superficial femoral artery and therefore ALP has been suggested as a surrogate for arterial stiffening. [5, 15]

We noted an independent association between higher ALP levels and ESRD. Apart from vascular calcification, arterial stiffness, as measured by central pressures (brachial-ankle pulse wave velocity) might contribute to the progression of CKD[16–18]. Proposed mechanism of renal damage from arterial stiffness include a) highly pulsatile blood pressure and flow to the low resistance renal vascular bed and b) defects in the filtration barrier leading to intraglomerular hypertension, hyperfiltration, and eventual nephrosclerosis. Beddhu et al. noted higher urinary protein excretion levels in those with higher ALP levels thereby contributing to the progression of kidney disease[8]. Even though similar results were seen in our study as well (table 1), we could not further examine the associations between ALP level and proteinuria in our study due to lack of adequate data, but might be examined in other future studies [19]. Higher ALP levels have also been associated with inflammation in CKD which may further contribute to the progression of kidney disease explaining these observed associations[8, 20].

The strength of our study stems from the validation of our CKD registry, large heterogeneous sample size, and the availability of both dialysis and mortality data that provided us an opportunity to do competing risk analysis. Limitations of the analysis were the exclusion of patients with earlier stages of CKD with eGFR ≥ 60 ml/min/1.73 m^2 who had albuminuria and other structural abnormalities. We were unable to identify patients with

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

active liver disease which might account for markedly elevated ALP levels. However, to reduce confounding, we used multivariable analysis using ALT and AST and performed a sensitivity analysis within the reference range of ALP (0–149 U/L) which showed similar results. We also lacked data relating to 25-hydroxyvitamin D, parathyroid hormone, serum phosphorus, and proteinuria levels for the entire study population. However, our sensitivity analysis that included patients with available data for serum phosphorus, and proteinuria showed similar associations.

Bone-specific alkaline phosphatase (bALP), an isoenzyme of ALP, is a more sensitive and specific marker for bone histology than intact PTH and ALP alone. High serum bALP is associated with fracture risk and mortality in CKD and hemodialysis patients[21]. Few studies have reported that bALP is a better predictor of death than ALP in the hemodialysis population[22]. However, bALP is not routinely measured because the assay is not readily available and is expensive. Therefore, most large retrospective, observational studies such as this use ALP since it is inexpensive and frequently measured. Further, a recent analysis using NHANES data did not show an association between bALP and mortality in a non-dialysis-dependent CKD population[23].

In summary, elevated ALP levels are associated with an increased risk of ESRD and all cause mortality in patients with CKD stages 3–4. These findings, along with previous studies in this area, suggest that clinicians may use ALP as a risk assessment tool to identify patients with higher risk for mortality and/or ESRD progression. More studies are warranted to confirm the association of ALP with ESRD and illuminate the pathogenetic process.

Acknowledgments

We thank other members of the Cleveland Clinic CKD registry (John Sharp; Stacey E. Jolly, MD; Vicky Konig; Welf Saupe; and Jennifer Hyland, CNP) for their contributions to the CKD registry development and maintenance.

Support: SDN is supported by a career development award from the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health (NIH; grant RR024990). JVN is supported by DK094112. JDS is supported by NIH/National Institute of Diabetes and Digestive and Kidney Diseases (R01 DK085185 and DK094112) and investigator initiated-grant support from Genzyme Corporation, NIH/National Institute of Mental Health (P60MD00265), Health Services and Resources Administration (1R39OT22056), the Centers for Disease Control and Prevention, and Genzyme and Roche Organ Transplant Research Foundation. The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. The creation of the CKD registry was funded by an unrestricted grant from Amgen, Inc. to the Department of Nephrology and Hypertension Research and Education Fund.

References

1. Jono S, Shioi A, Ikari Y, Nishizawa Y. Vascular calcification in chronic kidney disease. J Bone Miner Metab. 2006; 24(2):176–181. [PubMed: 16502129]
2. Kalantar-Zadeh K, Shah A, Duong U, Hechter RC, Dukkipati R, Kovesdy CP. Kidney bone disease and mortality in CKD: Revisiting the role of vitamin D, calcimimetics, alkaline phosphatase, and minerals. Kidney Int Suppl. 2010; (117):S10–21. [PubMed: 20671739]
3. Abramowitz M, Muntner P, Coco M, et al. Serum alkaline phosphatase and phosphate and risk of mortality and hospitalization. Clin J Am Soc Nephrol. 2010; 5(6):1064–1071. [PubMed: 20378645]
4. Tonelli M, Curhan G, Pfeffer M, et al. Relation between alkaline phosphatase, serum phosphate, and all-cause or cardiovascular mortality. Circulation. 2009; 120(18):1784–1792. [PubMed: 19841303]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

5. Shantouf R, Kovesdy CP, Kim Y, et al. Association of serum alkaline phosphatase with coronary artery calcification in maintenance hemodialysis patients. Clin J Am Soc Nephrol. 2009; 4(6):1106–1114. [PubMed: 19423565]
6. Regidor DL, Kovesdy CP, Mehrotra R, et al. Serum alkaline phosphatase predicts mortality among maintenance hemodialysis patients. J Am Soc Nephrol. 2008; 19(11):2193–2203. [PubMed: 18667733]
7. Blayney MJ, Pisoni RL, Bragg-Gresham JL, et al. High alkaline phosphatase levels in hemodialysis patients are associated with higher risk of hospitalization and death. Kidney Int. 2008; 74(5):655–663. [PubMed: 18547993]
8. Beddhu S, Ma X, Baird B, Cheung AK, Greene T. Serum alkaline phosphatase and mortality in african americans with chronic kidney disease. Clin J Am Soc Nephrol. 2009; 4(11):1805–1810. [PubMed: 19729429]
9. Kovesdy CP, Ureche V, Lu JL, Kalantar-Zadeh K. Outcome predictability of serum alkaline phosphatase in men with pre-dialysis CKD. Nephrol Dial Transplant. 2010; 25(9):3003–3011. [PubMed: 20299338]
10. Kidney Disease. Improving Global Outcomes (KDIGO) CKD-MBD Work Group: KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl. 2009; (113):S1–130.
11. Navaneethan SD, Jolly SE, Schold JD, et al. Development and validation of an electronic health record-based chronic kidney disease registry. Clin J Am Soc Nephrol. 2011; 6(1555–905; 1):40–49. [PubMed: 21051745]
12. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150(9):604–612. [PubMed: 19414839]
13. Lomashvili KA, Garg P, Narisawa S, Millan JL, O'Neill WC. Upregulation of alkaline phosphatase and pyrophosphate hydrolysis: Potential mechanism for uremic vascular calcification. Kidney Int. 2008; 73(9):1024–1030. [PubMed: 18288101]
14. Nitta K. Vascular calcification in patients with chronic kidney disease. Ther Apher Dial. 2011; 15(6):513–521. [PubMed: 22107687]
15. Sigrist MK, Taal MW, Bungay P, McIntyre CW. Progressive vascular calcification over 2 years is associated with arterial stiffening and increased mortality in patients with stages 4 and 5 chronic kidney disease. Clin J Am Soc Nephrol. 2007; 2(6):1241–1248. [PubMed: 17928470]
16. Chen SC, Chang JM, Liu WC, et al. Brachial-ankle pulse wave velocity and rate of renal function decline and mortality in chronic kidney disease. Clin J Am Soc Nephrol. 2011; 6(4):724–732. [PubMed: 21454721]
17. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: Cause and logic of therapy. Hypertension. 2005; 46(1):200–204. [PubMed: 15911742]
18. Cohen DL, Townsend RR. Central blood pressure and chronic kidney disease progression. Int J Nephrol. 2011; 2011:407801. [PubMed: 21423561]
19. Hermans MM, Henry R, Dekker JM, et al. Estimated glomerular filtration rate and urinary albumin excretion are independently associated with greater arterial stiffness: The hoorn study. J Am Soc Nephrol. 2007; 18(6):1942–1952. [PubMed: 17460143]
20. Damera S, Raphael KL, Baird BC, Cheung AK, Greene T, Beddhu S. Serum alkaline phosphatase levels associate with elevated serum C-reactive protein in chronic kidney disease. Kidney Int. 2011; 79(2):228–233. [PubMed: 20881941]
21. Fahrleitner-Pammer A, Herberth J, Browning SR, et al. Bone markers predict cardiovascular events in chronic kidney disease. J Bone Miner Res. 2008; 23(11):1850–1858. [PubMed: 18597636]
22. Drechsler C, Verduijn M, Pilz S, et al. Bone alkaline phosphatase and mortality in dialysis patients. Clin J Am Soc Nephrol. 2011; 6(7):1752–1759. [PubMed: 21597029]
23. Filipowicz R, Greene T, Wei G, et al. Associations of serum skeletal alkaline phosphatase with elevated C-reactive protein and mortality. Clin J Am Soc Nephrol. 2013; 8(1):26–32. [PubMed: 23124780]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

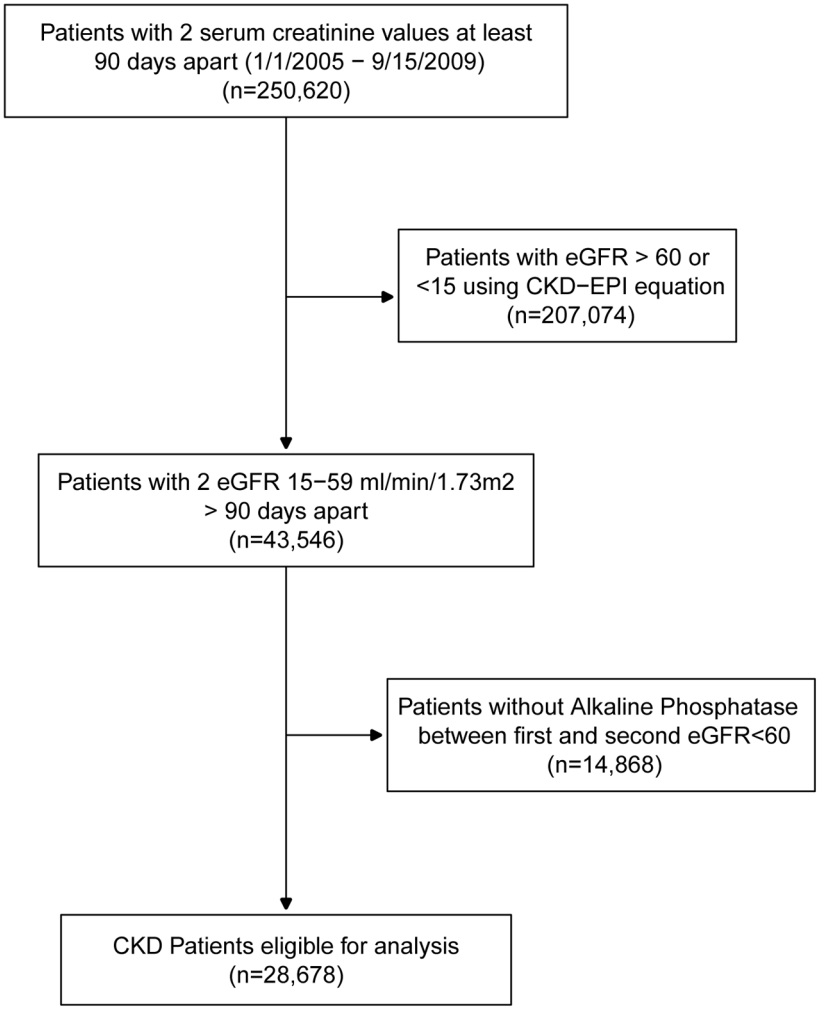

Figure 1.
Flow chart showing how patients were selected for this analysis.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

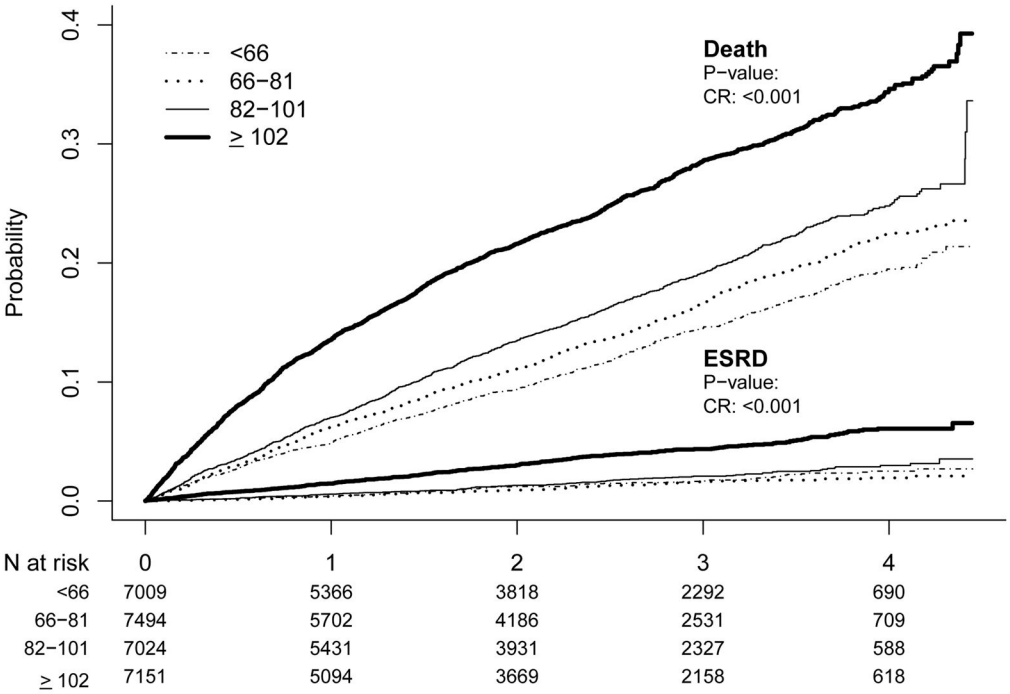

Figure 2.

Cumulative incidence curves for ESRD and all-cause mortality for those with different levels of alkaline phosphatase

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

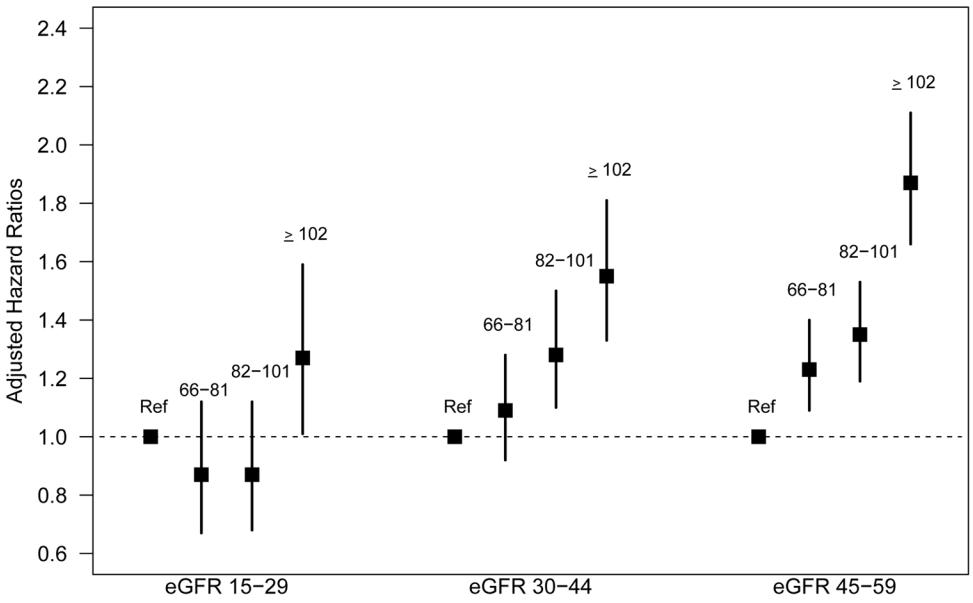

Figure 3.

Associations of ALP with mortality based on the stage of CKD

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1

Characteristics of patients with CKD stages 3–4with and without measured serum ALP levels

	Serum ALP				
	<66 U/L (n=7009)	**66–81 U/L (n=7494)**	**82–101 U/L (n=7024)**	**≥102 U/L (n=7151)**	**Missing data (n=14868)**
Age (y)	71.9±11.8	72.9±11.4	72.9±11.6	70.2±12.8	74.0±11.2
Male sex	3515(50.1)	3454(46.1)	3055(43.5)	3146(44.0)	6432(43.3)
African American	707(10.1)	831(11.1)	856(12.2)	1118(15.6)	1701(11.4)
eGFR (ml/min/1.73 m^2)	48.3±9.8	48.0±9.9	47.1±10.3	45.5±11.2	46.2±10.5
Stage of CKD					
Stage 3a^	4891(69.8)	5147(68.7)	4514(64.3)	4231(59.2)	9158(61.6)
Stage 3b^	1686(24.1)	1849(24.7)	1920(27.3)	2088(29.2)	4305(29.0)
Stage 4^	432(6.2)	498(6.6)	590(8.4)	832(11.6)	1405(9.4)
Body mass index (kg/m^2)*	28.6±5.7	29.0±6.1	29.3±6.4	29.3±7.0	29.5±6.6
Body mass index category					
<18.5 kg/m^2	93(1.3)	89(1.2)	77(1.1)	114(1.6)	150(1.0)
18.5–24.9 kg/m^2	1728(24.7)	1760(23.5)	1614(23.0)	1823(25.5)	3178(21.4)
25–29.9 kg/m^2	2583(36.9)	2702(36.1)	2472(35.2)	2333(32.6)	4698(31.6)
≥30 kg/m^2	2333(33.3)	2650(35.4)	2552(36.3)	2588(36.2)	5239(35.2)
Missing	272(3.9)	293(3.9)	309(4.4)	293(4.1)	1603(10.8)
Smoking					
No	5734(81.8)	6075(81.1)	5611(79.9)	5569(77.9)	9398(63.2)
Yes	395(5.6)	455(6.1)	491(7.0)	617(8.6)	926(6.2)
Missing	880(12.6)	964(12.9)	922(13.1)	965(13.5)	4544(30.6)
Diabetes	1569(22.4)	1570(21.0)	1422(20.2)	1648(23.0)	2927(19.7)
Hypertension	6272(89.5)	6732(89.8)	6283(89.5)	6261(87.6)	9897(66.6)
Coronary artery disease	1655(23.6)	1715(22.9)	1656(23.6)	1654(23.1)	1984(13.3)
Congestive heart failure	481(6.9)	579(7.7)	605(8.6)	847(11.8)	809(5.4)
Hyperlipidemia	5635(80.4)	5958(79.5)	5417(77.1)	5049(70.6)	10629(71.5)
Cerebrovascular disease	662(9.4)	691(9.2)	709(10.1)	678(9.5)	980(6.6)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

	Serum ALP				
	<66 U/L (n=7009)	**66–81 U/L (n=7494)**	**82–101 U/L (n=7024)**	**≥102 U/L (n=7151)**	**Missing data (n=14868)**
Malignancy	1978(28.2)	2057(27.4)	1996(28.4)	2120(29.6)	2074(13.9)
ACEi/ARB use	4593(65.5)	4839(64.6)	4471(63.7)	4381(61.3)	8051(54.1)
Statin use	4195(59.9)	4428(59.1)	4127(58.8)	3769(52.7)	6992(47.0)
Hemoglobin (g/dl)*	12.9±1.7	13.0±1.8	12.9±1.7	12.4±1.9	12.8±1.8
Serum albumin (g/dl)*	4.2±0.37	4.2±0.38	4.1±0.40	4.0±0.52	3.8±0.58
AST (IU/L)*	23.0[19.0–27.0]	23.0[19.0–27.0]	23.0[19.0–27.0]	24.0[19.0–33.0]	22.0[18.0–27.0]
ALT (IU/L)*	17.0[13.0–22.0]	16.0[13.0–22.0]	16.0[13.0–22.0]	18.0[13.0–27.0]	30.0[18.0–38.0]
Serum bilirubin (mg/dl)*	0.50[0.30–0.60]	0.50[0.30–0.60]	0.50[0.30–0.60]	0.50[0.30–0.70]	0.50[0.38–0.70]
Serum bicarbonate (mEq/L)*	26.2±3.0	26.2±3.1	26.0±3.3	25.3±3.7	26.7±3.3
Intact PTH (pg/ml)*	50.0[30.0–78.0]	55.0[34.0–94.0]	64.0[42.0–105.0]	69.0[41.0–120.0]	62.0[41.0–106.0]
Serum phosphorus (mg/dl)*	3.5±0.69	3.5±0.75	3.5±0.74	3.6±0.77	3.5±0.78
Proteinuria*	818(23.2)	848(22.8)	887(26.3)	1171(33.6)	1863(27.7)
Calcium (mg/dl)*	9.6±0.55	9.6±0.56	9.6±0.59	9.5±0.64	9.4±0.60

Note: Values for categorical variables are given as number (percentage) with Cochran-Armitage trend test on variables with two levels across quartiles, or Pearson's chi-square test on all other categorical variables and between those with and without missing data; values for continuous variables are given as mean ± standard deviation with analysis of variance or median [interquartile range] with Kruskal-Wallis test. All comparisons significantly different across quartiles except diabetes, coronary artery disease, cerebrovascular disease, and serum phosphorus. Cochran-Armitage positive statistic for African-American, heart failure, malignancy and proteinuria. Cochran-Armitage negative statistic for gender, hypertension, hyperlipidemia, ACEi/ARB, statin. All comparisons significantly different between patients with and without data except hemoglobin level. Conversion factors for units: bilirubin in mg/dL to μmol/L, x17.1; phosphorus in mg/dL to mmol/L, x0.3229; calcium in mg/dL to mmol/L, x0.2495.

*Data not available for all subjects. Missing values among patients included in the study: Body mass index = 1167 (4%), smoking = 3731 (13%), Hemoglobin = 2063 (7%), Serum albumin = 296 (1%), AST = 284 1(%), ALT = 224 (0.8%), Serum bilirubin = 301 (1%), Serum bicarbonate =51 (<0.5%), Intact PTH = 25690 (90%), serum phosphorus=23011 (80%), Proteinuria = 14562 (51%), Calcium=52 (<0.5%). Missing values among patients not included in the study due to missing ALP: Body mass index = 1603 (11%), Hemoglobin =4615 (31%), Serum albumin = 7753 (52%), AST =5648 (38%), ALT = 3590 (24%), Serum bilirubin = 6349 (43%), Serum bicarbonate =372 (3%), Intact PTH = 14011 (94%), serum phosphorus=12925 (87%), Proteinuria =8146 (55%), Calcium=379 (3%)., or N (%).

ALP, alkaline phosphatase; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PTH, parathyroid hormone;

^CKD stage 3a = eGFR 45–59 ml/min/1.73 m^2; stage 3b = eGFR 30–44 ml/min/1.73 m^2; stage 4 = eGFR 15–29 ml/min/1.73 m^2.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2

Associations between serum ALP levels and all-cause mortality and ESRD.

	All-cause mortality	ESRD
Categorical		
Q2 vs. Q1	1.12(1.02, 1.23)	0.82(0.61,1.09)
Q3 vs. Q1	1.26(1.15, 1.38)	1.00(0.76, 1.30)
Q4 vs. Q1	1.68(1.54, 1.83)	1.38(1.09, 1.76)
Continuous		
Each 1-SD higher ALP*	1.16(1.14, 1.18)	1.15(1.09, 1.22)

Note: Values given as **Adjusted HR (95% CI).** Pooled estimates from 5 imputed datasets.

Q1: <66 U/L, Q2: 66–81 U/L, Q3: 82–101 U/L, Q4: ≥102 U/L

Adjusted for age, gender, African American race, smoking, diabetes, hypertension, congestive heart failure, coronary artery disease, cerebrovascular disease, hyperlipidemia, malignancy, body mass index, Use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, use of statins, serum albumin, Hemoglobin, bicarbonate, estimated glomerular filtration rate, aspartate aminotransferase, alanine aminotransferase, bilirubin and calcium.

ALP, alkaline phosphatase; HR, hazard ratio; CI, confidence interval; ESRD, end-stage renal disease; Q, quartile; SD, standard deviation *1 SD is equivalent to 42.7 U/L