Exploring the impact of serum phosphate levels and hyperphosphatemia on renal outcomes: a real-world evidence study

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Background

- Chronic kidney disease (CKD) is a progressive condition associated with significant morbidity, mortality, and healthcare costs. [1,2].
- Hyperphosphatemia, a hallmark of CKD-mineral and bone disorder (CKD-MBD), is closely linked to vascular calcification, arterial stiffness, and increased cardiovascular mortality, particularly in hemodialysis patients. [3] Research highlights that even slight increases in serum phosphate levels significantly raise the risk of mortality. [4]
- Despite these associations, significant knowledge gaps remain regarding the prognostic significance of hyperphosphatemia and elevated serum phosphate levels, particularly among non-dialysis CKD patients in real-world clinical settings.
- Leveraging longitudinal data, our study aims to clarify the predictive roles of serum phosphate levels and hyperphosphatemia in renal outcomes. Improved understanding of these biomarkers may enhance risk stratification, inform personalized management strategies, and ultimately lead to more targeted interventions to improve patient outcomes.

Objective

- This study aimed to explore the impact of serum phosphate levels and hyperphosphatemia on renal outcomes in non-dialysis CKD patients.

Methods

- This prospective cohort study was conducted in the renal clinic of a tertiary care public teaching hospital. Adults with pre-dialysis CKD who had attended at least one face-to-face outpatient consultation and had two estimated glomerular filtration rate (eGFR) values <60 mL/min/1.73 m^2, recorded at least 90 days apart, were included. eGFR was calculated using the CKD-EPI creatinine equation.
- Patients aged <18 years, CKD stage V (eGFR <15 mL/min/1.73 m^2), requirement for dialysis or transplantation at baseline, or loss to follow-up were excluded. Hyperphosphatemia was defined as serum phosphate >4.5 mg/dL (normal range: 2.5–4.5 mg/dL).
- Participants were followed for at least 12 months or until death, dialysis initiation, kidney transplantation, or last available follow-up.
- The study analyzed the relationship between hyperphosphatemia, serum phosphate quartiles (Q1-Q4), continuous serum phosphate levels and renal outcomes, including mortality, composite endpoints (dialysis initiation, ESRD progression, doubling of serum creatinine).
- Survival analysis was conducted using Kaplan-Meier curves, Log-rank test, and Cox proportional hazards models to evaluate associations. Statistical significance was defined as p<0.05, using STATA.

Results

❖ Baseline Characteristics

- Among the 360 participants (mean age 53.74 ± 13.99 years), 137 (38.1%) had hyperphosphatemia, while 223 (61.9%) had normal serum phosphate levels. Compared to the normal phosphate group, individuals with hyperphosphatemia had significantly higher urea levels (94.71 ± 44.03 vs. 67.49 ± 37.16; p < 0.001) and lower hemoglobin levels (9.88 ± 2.13 vs. 11.25 ± 2.27; p < 0.001).
- There were no significant differences between groups in gender distribution (p = 0.081), age group (p = 0.287), diabetic CKD prevalence (p = 0.964), or BMI categories (p = 0.663).

Table 1: Impact of hyperphosphatemia on renal outcomes

Variables	Mortality	p-value	Composite endpoints*	p-value
	HR 95% CI		HR 95% CI	
Binary variable				
Hyperphosphatemia	2.59 (1.47-4.57)	**0.001**	2.55 (1.80-3.60)	**<0.005**
Hyperphosphatemia*	2.16 (1.13-4.14)	**0.020**	1.85 (1.26-2.73)	**<0.002**
Continuous variable				
Serum phosphate	1.20 (1.05-1.37)	**0.005**	1.20 (1.11-1.30)	**<0.005**
Serum phosphate*	1.10 (0.93-1.30)	0.222	1.05 (0.94-1.16)	0.322
Quartiles				
Serum Phosphate Q4 vs Q1	3.29 (1.51-7.16)	**0.003**	3.59 (2.15-5.99)	**<0.005**
Serum Phosphate Q3 vs Q1	1.55 (0.65-3.70)	0.318	1.93 (1.10-3.38)	**0.021**
Serum Phosphate Q2 vs Q1	0.57 (0.20-1.62)	0.297	1.14 (0.63-2.04)	0.652
Serum Phosphate Q4 vs Q1*	2.23(0.85-5.80)	0.099	1.95(1.06-3.61)	**0.032**

Serum Phosphate Quartile 1, N=98 (≤3.6 mg/dL); Serum P Quartile 2, N=96 (3.7-4.2.mg/dL); Serum P Quartile 3, N=79 (4.3-4.9 mg/dL); Serum P Quartile 4, N=87 ≥ 5.0 mg/dL). (Composite end points*; ESRD, Dialysis initiation, Double Serum Creatine from baseline). *Model adjusted for age, gender, urea, hemoglobin, and ALP.

❖ Impact of hyperphosphatemia and serum phosphate levels on renal outcomes

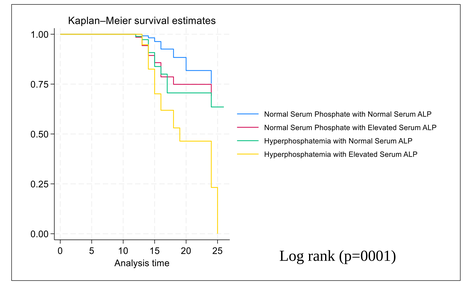
- The unadjusted Cox proportional hazards model demonstrated that hyperphosphatemia was significantly associated with a 2.59-fold increased risk of mortality and a 2.55-fold increased risk of reaching the composite renal endpoint. In the adjusted model, hyperphosphatemia remained a significant predictor, with a 2.16-fold increased risk of mortality and a 1.85-fold increased risk of composite renal outcomes.
- When serum phosphate was modeled as a continuous variable, a 20% increased hazard of mortality (HR=1.20, CI 95% 1.05-1.37, p=0.005) and a 20% increased hazard for composite endpoints (HR=1.20, CI 95% 1.11-1.30, p<0.005) were observed.
- Cox proportional hazards regression revealed a significant association between serum phosphate quartiles and mortality, with Q4 exhibiting over a threefold increased hazard of mortality (HR=3.29, CI 95% 1.51-7.16, p=0.003) and composite endpoints (HR=3.59, CI 95% 2.15-5.99, p<0.005).

❖ Incidence of mortality

- Overall, 50 participants (13.9%) died during the study period, with a higher mortality rate observed in the hyperphosphatemia group 29 (21.2%) compared to the normal phosphate group 21 (9.4%).
- The composite renal endpoint occurred in 135 participants (37.6%), with a higher incidence in the hyperphosphatemia group (57.4%) compared to the normal phosphate group (25.6%). Dialysis was initiated in 33.6% of participants with hyperphosphatemia versus 14.8% with normal phosphate levels; progression to ESRD occurred in 54.0% versus 23.3%; and doubling of serum creatinine in 48.2% versus 17.9%, respectively.

Results (contd.)

Fig 1: Subgroup analysis of hyperphosphatemia on mortality based on elevated serum ALP



- Kaplan–Meier survival estimates for serum phosphate levels stratified by serum ALP. Among the four groups, individuals with normal phosphate and normal ALP have the highest survival, while those with hyperphosphatemia and elevated ALP show the lowest survival. The other two groups display intermediate survival probabilities.

Conclusions

- This study demonstrates that hyperphosphatemia is a strong and independent predictor of both all-cause mortality and composite endpoints in non-dialysis CKD patients.
- These findings underscore the prognostic significance of hyperphosphatemia and highlight the need for early identification and targeted management of elevated phosphate levels to improve patient outcomes, slow CKD progression, and reduce overall healthcare burden.

References

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