Elevated levels of serum alkaline phosphatase (AlkPhos) have been reported to be associated with increased mortality risk in hemodialysis (HD) patients. We examined the association of serum AlkPhos with all-cause mortality in our PD patients. The study enrolled 90 PD patients beginning in 1995. On enrollment, demographics and clinical and biochemical data were recorded. Patients were followed to September 2011.

Mean age of the enrollees was 52 years, with 61% being women, and most (81%) being of African descent. Mean and median AlkPhos were 135 U/L and 113 U/L respectively. Mean and maximum follow-up were 2.61 and 16 years respectively. As expected, AlkPhos correlated directly with serum intact parathyroid hormone (r = 0.36, p = 0.003). In a Cox multivariate regression analysis with adjustment for confounding variables, AlkPhos as a continuous (relative risk: 1.016; p = 0.004) and a categorical variable [>120 U/L and ≤120 U/L (relative risk: 6.0; p = 0.03)] remained a significant independent predictor of mortality. For each unit increase in enrollment AlkPhos, there was a 1.6% increase in the relative risk of death.

Elevated serum AlkPhos is significantly and independently associated with increased mortality risk in our PD patients followed for up to 16 years. AlkPhos should be evaluated prospectively as a potential therapeutic target in clinical practice.

Key words
Peritoneal dialysis, alkaline phosphatase, parathyroid hormone, mortality

Introduction
Despite advances in dialysis therapy, mortality remains high for patients with end-stage renal disease.

According to 2012 U.S. Renal Data System (USRDS) report, mortality is twice as high among dialysis patients 65 years of age and older as it is among patients in the general population who have diabetes, cancer, congestive heart failure, cerebrovascular accident or transient ischemic attack, or acute myocardial infarction (1). Identification of various risk factors and aggressive risk factor modification are important strategies to improve outcomes in these patients.

Among the various risk factors, bone mineral disorders have been reported to be important factors contributing to increased mortality risk in both pre-dialysis chronic kidney disease and dialysis patients (2–4). Serum alkaline phosphatase (AlkPhos) is an enzyme that removes phosphate from proteins and nucleotides. It originates mainly in bone and liver. In patients with chronic kidney failure and associated hyperparathyroidism and renal osteodystrophy, serum AlkPhos concentration reflects bone activity, including bone turnover and bone metabolism (5). For example, elevated serum AlkPhos is seen in high turnover bone disease (6).

Elevated AlkPhos has been reported to be associated with progressive arterial calcification and increased mortality in pre-dialysis chronic kidney disease patients (7–9). AlkPhos is linked to vascular calcification and mortality in maintenance hemodialysis (HD) patients (10–12). In PD patients, AlkPhos has been reported to be a predictor of bone mineral density (13). Yeoh and Sivaraman reported that elevated serum AlkPhos affects the short-term survival of PD patients, but could not predict patient outcome (14). There is a paucity of data on whether serum AlkPhos is an independent predictor of long-term survival in PD patients.

Methods
The present study enrolled 90 PD patients beginning in 1995. On enrollment, demographics and clinical and biochemical data including AlkPhos were recorded. Patients were followed to September 2011.
**Statistical analysis**

Continuous variables are expressed as mean ± standard deviation. For selected comparisons between group means, parametric (t-test) or nonparametric tests (Mann–Whitney test) were used. Correlations are reported as either a Pearson correlation coefficient or a Spearman rank correlation coefficient. Observed survival was computed by the Kaplan–Meier method (15). The log-rank test was used to assess differences in the survival curves. Independent predictors of survival were determined by Cox regression analysis. Calculations were performed using the SPSS software application (version 12.0.1 for Windows: SPSS, Armonk, NY, U.S.A.).

This study was approved by the Institutional Review Board of State University of New York Downstate Medical Center University Hospital Brooklyn at Long Island College Hospital.

**Results**

Mean age of the patients was 52 ± 16 years, with 61% being women, most (81%) being of African descent, and 42% being diabetic. Mean, median, and maximum follow-up was 2.61, 1.60, and 16 years respectively. Enrollment mean and median AlkPhos were 135 U/L and 113 U/L respectively. The frequency distribution of AlkPhos was skewed. Elevated levels (greater than 104 U/L) were observed in 56% of the patients. As expected, AlkPhos correlated directly with intact parathyroid hormone ($r = 0.36$, $p = 0.003$).

Independent predictors of mortality were identified by a multivariate Cox proportional hazards analysis. Adjusting for age, race, sex, diabetes, hypertension, dialysis vintage at enrollment, albumin, albumin-corrected calcium, parathyroid hormone, creatinine, blood urea nitrogen, hemoglobin, iron, serum glutamic oxaloacetic transaminase, and white blood cell count, serum AlkPhos was an independent predictor of mortality (relative risk: 1.016; $p = 0.004$). Therefore, every unit increase in AlkPhos resulted in a 1.6% increased mortality risk. Other significant predictors of mortality were: albumin-corrected calcium (relative risk: 2.20; $p = 0.035$) and parathyroid hormone (relative risk: 0.998; $p = 0.02$; Table I). Analyses using log-transformed AlkPhos yielded similar results.

Based on previous observations in HD patients (10,11), we stratified PD patients into two groups: those with an AlkPhos greater than 120 U/L and with an AlkPhos of 120 U/L or less. In a Cox multivariate regression analysis with adjustment for the confounding variables listed earlier, serum AlkPhos as a categorical variable (relative risk: 6.0; $p = 0.03$) was an independent predictor of mortality. Compared with patients whose AlkPhos was 120 U/L or less, patients with an AlkPhos greater than 120 U/L had an all-cause mortality risk that was increased by a factor of 6.

**Discussion**

In this study, we demonstrated that higher serum AlkPhos activity was associated with increased mortality in our PD patients. To our knowledge, no information is available in the literature about the relationship between serum AlkPhos and long-term survival in PD patients. Yeoh and Sivaraman (14) reported that high serum AlkPhos affects short-term survival (first 6 months), but cannot predict patient outcomes in PD. It has also been reported that, in HD patients, higher serum AlkPhos is associated with increased mortality risk (3,11,12).

Using a Cox multivariate regression analysis, with adjustment for various confounding variables, we showed that, as a continuous variable, serum AlkPhos is a significant negative predictor of long-term survival in PD patients. Because the frequency distribution of AlkPhos was highly skewed, we also analyzed the data using log-transformed AlkPhos and observed similar results. Our finding that, as a categorical variable (>120 U/L vs. ≤120 U/L), serum AlkPhos is a strong independent predictor of mortality in PD patients agrees with previously published reports for HD patients (10,11).

Elevated serum AlkPhos is commonly associated with diseases of bone and liver. It is not clear how elevated AlkPhos mediates increased risk of mortality in PD patients. It has recently been reported that higher

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase</td>
<td>1.016</td>
<td>0.004</td>
</tr>
<tr>
<td>Albumin corrected calcium</td>
<td>2.20</td>
<td>0.035</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>0.998</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Other variables included in the model, but not statistically significant, were age, race, sex, diabetes, hypertension, dialysis vintage at enrollment, albumin, creatinine, blood urea nitrogen, hemoglobin, iron, aspartate aminotransferase, and white blood cell count.
serum AlkPhos is associated with risk of coronary artery disease and increased total mortality in elderly men (16). Higher AlkPhos has been reported to be associated with elevated C-reactive protein, a marker for inflammation (17,18). Shantouf et al. (10) reported an association between serum AlkPhos and calcification in HD patients. Prospective long-term studies are needed to investigate potential therapeutic interventions to modulate serum AlkPhos and outcomes in PD patients.

Conclusions
Higher serum AlkPhos at enrollment is independently associated with increased risk of mortality in PD patients. Serum AlkPhos should be routinely monitored. Factors affecting serum AlkPhos concentrations in PD patients should be investigated in more detail. Further studies are needed to elucidate the mechanisms of the increased mortality associated with higher serum AlkPhos and to examine whether interventions that lower serum AlkPhos improve survival in PD patients.

Disclosures
All the authors declare that no financial conflict of interest exists.

References

Corresponding author:
Paul A. Fein, md, Department of Medicine, Division of Nephrology, The Brooklyn Hospital Center, 121 DeKalb Avenue, Brooklyn, New York 11201 U.S.A.
E-mail: pafmd@juno.com