Serum inorganic phosphorus levels predict 30-day mortality in patients with community acquired pneumonia

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Abstract

Background: Community acquired pneumonia is a major cause of morbidity and mortality. The association between serum phosphorus levels on admission and the outcome of patients with community acquired pneumonia has not been widely examined. We aimed to investigate the prognostic value of serum phosphorus levels on admission on the 30-day mortality.

Methods: The cohort included patients of 18 years old or older who were diagnosed with community acquired pneumonia between 2006 and 2012. Patients were retrospectively analyzed to identify risk factors for a primary endpoint of 30-day mortality. Binary logistic regression analysis was used for the calculation of the odds ratios (OR) and p values in bivariate and multivariate analysis to identify association between patients' characteristic and 30-day mortality.

Results: The cohort included 3894 patients. In multivariate regression analysis, variables associated with increased risk of 30-day mortality included: age >80 years, increased CURB-65 score, RDW >15, hypernatremia >150 mmol/l, hypoalbuminemia <2 gr/dl and abnormal levels of phosphorus. Levels of <1.5 mg/dl and >4.5 mg/dl were significantly associated with excess 30-day mortality, 38 % (OR 2.9, CI 1.8-4.9, P = 0.001) and 39 % (OR 3.4, CI 2.7-4.2, P = 0.001), respectively. Phosphorus levels within the upper normal limits (4-4.5 mg/dl) were associated with higher mortality rates compared to levels between 1.5-3.5 mg/dl, the reference group, 24 % (OR 1.9, CI 1.5-2.4, P = 0.001).

Conclusions: Abnormal phosphorus levels on admission are associated with increased mortality rates among patients hospitalized with Community acquired pneumonia.

Background

Community acquired pneumonia (CAP) is among the leading causes of mortality and severe morbidity especially among elderly population. Despite the efficacy of modern antibiotic treatment, it still ranks as the sixth most common cause of death [1–3]. Prognostic scores, like the CURB65 score and the Pneumonia Patient Outcomes Research Team score, were developed to estimate the risk of adverse outcome in patients treated in emergency rooms in an attempt to determine who is at risk for an adverse outcome, and therefore should be hospitalized [4, 5].

Phosphorus, as an essential component in the ATP molecule, plays a central role in the energy production. Serum phosphorus level disturbances in patients with pneumonia have been reported [6–9]. Hypophosphatemia is detected in 2–3 % of the patients hospitalized with medical illness [10–12]. Commonly reported etiologies for hypophosphatemia include alcohol abuse and withdrawal, diabetic ketoacidosis, nutritional recovery, alkalotic states, accelerated erythropoiesis and gram negative sepsis [13–19]. Many drugs have also been reported to cause hypophosphatemia, the most common being methylprednisolone, epinephrine, albumin, terbutaline, theophylline, and diethylstilbestrol [20].

Hypophosphatemia is known to play an essential role in impaired chemotaxis, phagocytosis, and bactericidal activity of macrophages [21]. Hypophosphatemia can lead to...
ATP depletion, a shift from oxidative phosphorylation toward glycolysis, and subsequently, organ dysfunction and muscle weakness. Fisher et al. found hypophosphatemia to be associated with longer hospital stay, but not with higher mortality in patients with respiratory illness [7]. Sankaran et al., on the other hand, reported that hypophosphatemic patients with pneumonia had longer hospital stay and higher mortality when compared with normophosphatemic patients [6].

In contrast to hypophosphatemia, the association between hyperphosphatemia and pneumonia has not been widely studied. Severe hyperphosphatemia may result in hypocalcemia which can cause tetany and pulmonary calcification. Saldias et al. showed that hyperphosphatemia on admission represents a prognostic factor for in-hospital mortality in elderly patients with community acquired pneumonia [9].

In this cohort study, we aimed to examine the predictive prognostic value of serum phosphorus level on admission on the 30-day mortality in patients with community acquired pneumonia.

### Methods

Patients aged 18 years old or older who were diagnosed with CAP and admitted to Rambam Health Care Campus, a tertiary medical center, between 1 January, 2006 and 31 December, 2012 were retrospectively and consecutively analyzed to identify risk factors for 30-day mortality. CAP was defined as pneumonia identified within the first 48 hours of hospitalization. The diagnosis of pneumonia was confirmed when the patient fulfilled the criteria suggested by Fang [22]. These criteria are as follows:

- a) infiltrate in a chest x-ray taken on admission;
- b) the presence of one or more major findings (cough, mucopurulent or hemoptic expectoration, axillary temperature of over 37.8 °C); or
- c) at least two minor findings (pleuritic chest pain, dyspnea, decreased level of consciousness, lung tissue condensation observed in the physical lung examination, or a white blood count of over 12 000/mL).

Protocol for treatment of CAP included either a combination of Ceftriaxone and Azithromycin or Levofloxacin as monotherapy. Data were collected from the Prometheus, an integrated computer system for handling patients’ medical records. The 30-day mortality data were

### Table 1: Bivariate analysis of patients’ characteristics associated with 30-day mortality

| Clinical RISK Factors | 30-day-mortality | P-value | OR   | 95 % CI |
|-----------------------|------------------|---------|------|--------|
|                       | Number %         | Number %|       |        |
| Gender                |                  |         |      |        |
| Female                | 1664             | 674     | 17 % | Ref.   |
| Male                  | 2212             | 392     | 18 % | .529   | 1.056 | .892 | 1.249 |
| Age                   |                  |         |      |        |
| <45                   | 271              | 13      | 5 %  | .000   | Ref.   |
| 45-54                 | 209              | 12      | 6 %  | .252   | 1.490 | .753 | 2.947 |
| 55-64                 | 356              | 30      | 8 %  | .001   | 2.611 | 1.479 | 4.610 |
| 65-74                 | 579              | 74      | 13 % | .000   | 3.187 | 1.876 | 5.416 |
| 75-84                 | 1016             | 163     | 16 % | .000   | 5.387 | 3.247 | 8.936 |
| ≥85                   | 1445             | 382     | 26 % | .000   | 8.864 | 5.326 | 14.753 |
| Year                  |                  |         |      |        |
| 2006-2008             | 1730             | 289     | 17 % | .230   | Ref.   |
| 2009-2010             | 1058             | 202     | 19 % | .109   | 1.177 | .965 | 1.435 |
| 2011-2012             | 1088             | 183     | 17 % | .937   | 1.008 | .823 | 1.235 |
| Charson’s             |                  |         |      |        |
| No illnesses          | 599              | 57      | 9.5 %| .000   | 1      |
| 1                     | 616              | 102     | 16.6 %| .000  | 2.511 | 1.625 | 3.882 |
| 2                     | 612              | 138     | 22.5 %| .000  | 3.361 | 2.203 | 5.129 |
| 3-4                   | 1105             | 326     | 29.5 %| .000  | 4.983 | 3.377 | 7.355 |
| 5-7                   | 723              | 245     | 33.9 %| .000  | 5.291 | 3.541 | 7.906 |
| 8+                    | 239              | 108     | 45.2 %| .000  | 8.678 | 5.522 | 13.637 |
| CURB-65               |                  |         |      |        |
| 0                     | 589              | 11      | 2 %  | .000   | Ref.   |
| 1                     | 881              | 76      | 9 %  | .000   | 4.961 | 2.613 | 9.420 |
| 2                     | 1286             | 192     | 15 % | .000   | 9.222 | 4.981 | 17.073 |
| 3                     | 826              | 257     | 31 % | .000   | 23.733 | 12.838 | 43.875 |
| 4                     | 263              | 120     | 46 % | .000   | 44.094 | 23.157 | 83.959 |
| 5                     | 31               | 18      | 58 % | .000   | 72.755 | 27.708 | 184.387 |

Abbreviations: OR Odds Ratio, CI Confidence Interval, Ref. Reference
| Parameter                  | 30 day- mortality | P-Value | OR       | 95 % CI     |
|----------------------------|-------------------|---------|----------|-------------|
|                            | Number            | %       | N        |             |
| BUN (mg/dL)                | <20               | 2754    | 71 %     | 298 11 %    | 28 % .000 | 3.15 2.494 3.970 |
|                            | 20-39             | 485     | 13 %     | 134 28 %    | .000      | 3.64 2.838 4.666 |
|                            | 40-59             | 382     | 10 %     | 117 31 %    | .000      | 3.64 2.838 4.666 |
|                            | ≥60               | 255     | 7 %      | 125 49 %    | .000      | 7.92 6.029 10.416 |
| Creatinine (mg/dL)         | 0.9-1.29          | 2258    | 58 %     | 288 13 %    | .000      | 3.399 2.708 4.266 |
|                            | 0.1-0.9           | 142     | 4 %      | 27 19 %     | .034      | 1.606 1.037 2.486 |
|                            | 1.3-1.49          | 545     | 14 %     | 95 17 %     | .004      | 1.444 1.121 1.861 |
|                            | 1.5-1.9           | 455     | 12 %     | 106 23 %    | .000      | 2.078 1.618 2.668 |
|                            | ≥2                | 476     | 12 %     | 158 33 %    | .000      | 2.46 2.012 3.028 |
| Hemoglobin                 | ≥12               | 1191    | 49 %     | 235 12 %    | .000      | 1.664 1.404 1.972 |
|                            | 10-11             | 1307    | 34 %     | 243 12 %    | .000      | 1.664 1.404 1.972 |
|                            | 9-10              | 380     | 10 %     | 99 26 %     | .000      | 2.819 2.222 3.577 |
|                            | <9                | 269     | 7 %      | 95 35 %     | .000      | 5.090 3.899 6.644 |
| Albumin (g/dL)             | 3.4-4             | 513     | 13 %     | 21 4 %      | .000      | 22.76 14.018 36.963 |
|                            | <2                | 347     | 9 %      | 171 49 %    | .000      | 22.76 14.018 36.963 |
|                            | 2-3               | 1668    | 43 %     | 313 19 %    | .000      | 5.41 3.438 8.519  |
|                            | 3-3.4             | 721     | 19 %     | 55 8 %      | .012      | 1.93 1.155 3.242  |
|                            | Missing           | 627     | 16 %     | 114 18 %    | .000      | 5.21 3.217 8.427  |
| Sodium (mmol/L)            | ≤130              | 412     | 11 %     | 76 18 %     | .000      | 1.00            |
|                            | 130-150           | 3366    | 87 %     | 543 16 %    | .231      | 0.85 0.652 1.109  |
|                            | ≥150              | 97      | 3 %      | 55 57 %     | .000      | 5.79 3.609 9.287  |
|                            | Missing           | 1       | 0 %      | 0 0 %       | .000      | 1.00            |
| WBC (10^3/μL)              | 4 ≤ ≤ 12          | 1816    | 47 %     | 259 14 %    | .000      | 22.76 14.018 36.963 |
|                            | <4                | 144     | 4 %      | 27 19 %     | .007      | 1.668 1.150 2.421 |
|                            | >12               | 1907    | 49 %     | 386 20 %    | .000      | 1.529 1.315 1.777 |
|                            | Missing           | 9       | 2 %      | 22 %        | .000      | 1.00            |
| Hematocrit (%)             | ≥30               | 3268    | 85 %     | 496 15 %    | Ref.      | 1.00            |
|                            | <30               | 599     | 15 %     | 176 29 %    | .000      | 2.735 2.280 3.280 |
|                            | Missing           | 9       | 2 %      | 22 %        | .000      | 1.00            |
| RDW (%)                    | ≤15               | 1958    | 59 %     | 242 12 %    | 1.00      | 1.00            |
|                            | >15               | 1373    | 41 %     | 348 25 %    | .000      | 2.41 2.008 2.886 |
|                            | Missing           | 545     | 84 %     | 15 %        | .000      | 1.00            |
| GFR (ml/min)               | ≤90               | 852     | 22 %     | 106 12.4 %  | .000      | 1.00            |
|                            | 60-90             | 1227    | 32 %     | 149 12.1 %  | .839      | 0.97 0.746 1.269 |
|                            | 30-60             | 1332    | 34 %     | 260 19.5 %  | .000      | 1.71 1.337 2.180 |
|                            | 15-30             | 369     | 10 %     | 130 35.2 %  | .000      | 3.83 2.850 5.141 |
|                            | <15               | 96      | 2 %      | 29 30.2 %   | .000      | 3.05 1.883 4.927 |
| Phosphorus (mg/dL)         | 2.5-4.49          | 2790    | 72 %     | 415 14.9 %  | .000      | 1.00            |
|                            | 2.2-4.9           | 643     | 17 %     | 91 14.2 %   | .641      | 0.94 0.738 1.205 |
|                            | ≥4.5              | 443     | 11 %     | 168 37.9 %  | .000      | 3.50 2.810 4.350 |
|                            | 1.51-3.9          | 3004    | 78 %     | 396 13.2 %  | .000      | 1.00            |
retrieved from the database of our hospital and the ministry of health. Exclusion criteria included age under 18 years, transfer from another hospital, hospitalization during 30 days prior to admission, hospital-acquired pneumonia (defined as pneumonia which was diagnosed more than 48 hours after admission) or partial antibiotic treatment before hospitalization.

The following data were retrieved from the electronic medical records of the patients:

1. Malignancies: solid tumors and hematologic malignancies. 2. Pulmonary diseases: bronchial asthma, chronic obstructive lung disease, interstitial lung disease, bronchiectasis, permanent tracheostomy, past history of thoracic radiotherapy, previous episode of pneumonia, and previous or current active smoker. 3. Immune suppression conditions: current chronic corticosteroid treatment, current or recent chemotherapy treatment, carrier of HIV, primary immune deficiency, history of bone marrow transplantation. 4. Cardiovascular diseases including patients with decompensated heart failure. 5. Chronic kidney disease including patients on dialysis. 6. Diabetes mellitus. 7. Liver cirrhosis. 8. Prior neurologic damage. 9. Chronic alcohol use. 10. Intravenous drug abuse. 11. Nursing house residents. The vital signs including heart rate, systolic blood pressure, respiratory rate, oxygen saturation and temperature were recorded on admission. The Charlson’s comorbidity index was calculated based on the data collected. The Charlson’s comorbidity index is a score that predicts the ten-year mortality for a patient who may have a range of comorbid conditions, (a total of 22 conditions), while each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each condition. Scores are summed to provide a total score to predict mortality [23].

**Laboratory variables on admission**

Serum glucose, serum creatinine, sodium, hemoglobin, white blood count, Red blood cell Distribution width (RDW), pH, calcium, phosphorus, bicarbonate, partial pressure of CO2, lactate, blood urea nitrogen (BUN), and serum albumin were measured on admission.

Hemoglobin levels, mean corpuscular volume and RDW were measured on admission, using the Advia 120 Hematology Analyzer (Siemens Healthcare Diagnostics Deerfield, Illinois, USA). Glucose, BUN and creatinine levels were measured using the “Dimension” (Siemens Healthcare Diagnostics Deerfield, Illinois, USA). The normal serum inorganic phosphorus range in the Rambam Health Care Campus laboratory is 2.5-4.5 mg/dl. Hypophosphatemia is defined as levels below 2.5 mg/dl; whereas, levels above 4.5 mg/dl defines hyperphosphatemia.

**Statistical analysis**

Bivariate logistic regression analysis was used for the calculation of the odds ratios (OR) with 95 % Confidence Interval (CI) and P values in bivariate analysis to identify association between patient’s characteristic and 30-day mortality. Multivariate forward stepwise logistic regression was performed to assess the relation between patient’s characteristics: co-morbidities, laboratory results, and 30-day mortality.

Variables were selected as candidates for the multivariate analysis on the basis of the level of significance of the bivariate association with 30-day mortality (P < 0.1). Notably, there was no predilection in choosing serum phosphorus or any other variable in the statistical model.

The area under curve (AUC) was used as a measure of model of discrimination. The calibration of the prediction equation was assessed by comparing the observed and expected numbers of 30-day mortality. The Hosmer-Lemeshow goodness-of-fit statistic was calculated. We calculated the Spearman’s rank correlation coefficient to try to find out any correlation between variables that were found positive in the multivariate analysis. Two-tailed P values of 0.05 or less were considered as statistically significant. All statistical analyses were performed using SPSS (Statistics Products Solutions Services; Armonk, New York, USA) 21.0 software for Windows; Redmond, Washington, USA.

The Rambam Hospital Institutional Review Board approved the study. The approval number is 0515-12-RMB. The need for informed consent was waived.

**Results**

Of the 5608 patients who were diagnosed with CAP in Rambam Health Care Campus between January 1, 2006 and December 31, 2012; 3876 patients had serum inorganic phosphorus levels were available within the first 24 hours of admission, and subsequently constituted our cohort. Of these 3876 patients, 57 % were males with median age of 69.6 years. The 30-day mortality was 17 % (n = 674). As shown in Table 1, the 30-day mortality was

### Table 2 Bivariate analysis of laboratory parameters associated with 30-day mortality (Continued)

| Phosphorus (mg/dl) | ≤1.5 | 62 | 2 % | 24 | 38.7 % | 0.00 | 4.16 | 2.468 | 7.009 |
|--------------------|------|----|-----|----|---------|------|------|--------|-------|
| Phosphorus (mg/dl) | 4-4.49 | 367 | 9 % | 86 | 23.4 % | 0.00 | 2.02 | 1.548 | 2.624 |
| Phosphorus (mg/dl) | ≥4.5 | 443 | 11 % | 168 | 37.9 % | 0.00 | 4.02 | 3.232 | 5.009 |

Abbreviations: OR Odds Ratio, CI Confidence Interval, Ref. Reference, BUN Blood Urea Nitrogen, WBC White Blood Cells, RDW Red Blood Cell Distribution Width, GFR Glomerular Filtration Rate
not significantly different between men and women. As well, the 30-day mortality each year was similar throughout the study period.

Factors associated with 30-day mortality
As depicted in Table 1; 674 patients died within 30 days. Patients who died were older and had higher Charlson's score reflecting more comorbid conditions. The year of diagnosis and inclusion did not influence the rate of 30-day mortality.

Table 2 shows the association between different laboratory parameters and 30-day mortality. When serum phosphorus levels were examined according to the normal laboratory range of our institution, that is, between 2.5 and 4.5 mg/dl and levels below 2.5 mg/dl representing hypophosphatemia and levels above 4.5 mg/dl representing hyperphosphatemia; only hyperphosphatemia, but not hypophosphatemia, was associated with increased mortality risk with odds ratio (OR), 95 % confidence interval (CI) and P value as follows: OR-3.5 (95 % CI 2.81-4.35, P <0.0001). According to the ROC curve, cutoff levels of 1.51 and 3.9 as our new reference. Accordingly, the 30-day mortality rate was 13.2 % and increased to 38.7 % 30-day mortality rate with OR-4.16 (95 % CI 2.468-7.009, P <0.0001) in patient with levels ≤1.5 mg/dl. Notably, levels between 4-4.49 mg/dl and ≥4.5 mg/dl were associated with 23.4 % and 37.9 % 30-day mortality rate with OR-2.02 (95 % CI 1.548-2.624, P < 0.0001) and OR-4.02 (95 % CI 3.232-5.009, P < 0.0001), respectively. Figure 2 shows the correlation between different serum phosphorus levels and 30-day mortality.

Relationship between Glomerular Filtration Rate (GFR), Phosphorus and Mortality
As shown in Fig. 3, the predictive value of serum phosphorus levels on CAP outcome was maintained even after adjustment for GFR. Through all levels of GFR, hypophosphatemia and hyperphosphatemia were associated with increased mortality rates.

Figure 1 shows the correlation between different serum phosphorus levels and 30-day mortality.
associated with excess of mortality rates, severe hypophosphatemia and hyperphosphatemia were further associated with increased mortality rates for each CURB-65 score (Fig. 4).

Relationship between Blood Urea Nitrogen (BUN), Phosphorus and Mortality

As shown in Fig. 5, the predictive value of serum phosphorus levels on CAP outcome was maintained even after adjustment for BUN. Through all levels of BUN, hypophosphatemia and hyperphosphatemia were associated with increased mortality rates.

Multivariate analysis of factors associated with 30-day mortality

As shown in Table 3, the following factors were associated with higher rates of 30-day mortality: sodium >150 meq/l, RDW >15, low albumin levels (<2) and age >80 years. Increasing CURB-65 scores were associated with higher mortality. Whenever serum phosphorus levels were added to the model, severe hypophosphatemia ((<1.5 mg/dl), levels between 4 and 4.5 mg/dl, and especially levels above 4.5 mg/dl were associated with significant mortality. The addition of serum phosphorus levels to the model improved AUC/ROC curve from 0.747 (95 % CI = 0.726-0.769) to 0.764 (95 % CI = 0.743-0.786). The Hosmer-Lemeshow goodness-of-fit statistic was not statistically significant (p = 0.77) indicating little departure and a perfect fit in both models.

In order to check for a possible correlation between serum phosphorus levels and other parameters, the spearman's correlation coefficient was calculated; however no significant correlation was found (Table 4).

Discussion

In this study, we examined the role of serum phosphorus levels as a predictor of 30-day mortality in patients admitted to medical wards because of CAP. Our study demonstrated that serum phosphorus level obtained within 24 hours from admission can predict 30-day mortality, with levels below 1.5 mg/dl and levels above 4.5 mg/dl being associated with increased mortality levels. It is remarkable to note that when we followed the conventional international definitions for hyperphosphatemia (>4.5 mg/dl) and hypophosphatemia (<2.5 mg/dl), only
Hyperphosphatemia was associated with increased mortality. However, when levels between 1.5-3.9 mg/dl constituted our reference group with 30-day mortality of 13.2 %, levels below 1.5 mg/dl and above 4.5 mg/dl were both associated with increased 30-days mortality, 38.7 % and 37.9 %, respectively. Notably, even levels between 4-4.49 mg/dl, that are considered to be normal according to laboratory standards, were associated with 23.4 % 30-day mortality rates.

Phosphorus, as an essential component in the ATP molecule, plays a central role in the energy production. Therefore, depleted phosphorus stores, reflected by hypophosphatemia, might lead to insufficient and reduced ATP production which subsequently impairs several vital systemic functions including the immune system and the ability of the lungs to clear edema [24]. Craddock et al have shown that severe hypophosphatemia causes acquired phagocyte dysfunction reflected by defected chemotaxis, phagocytosis and bactericidal activity [21].

Hypophosphatemia in the setting of acute infectious illness such as CAP might have several etiologies, including refeeding, insulin therapy, acute respiratory alkalosis, inadequate intake, decreased phosphorus absorption.
and the use of medications (eg. methylprednisolone, epinephrine, terbutaline, and theophylline) [13–20]. On the contrary, the causes of hyperphosphatemia in the acute setting of CAP are very few and usually include acute renal failure, phosphorus-containing medications and lactic or ketoacidosis. Di Marco et al have reported that high phosphorus levels can impair endothelial cell function at several levels including induction of sustained stiffening, increased apoptosis, impaired angiogenesis, impaired cell migration, downregulation of extracellular annexin II expression and shedding of endothelial microparticles [25]. Altogether, this suggests that hyperphosphatemia can interfere with normal function of the immune system.

Our study demonstrated that increased serum creatinine and urea levels were also associated with increased 30-day mortality, therefore, we aimed to examine whether the association between serum phosphorus levels and 30-day mortality is significant. We performed a multivariate analysis using the CURB-65 score, albumin, red blood cell distribution width (RDW), sodium, phosphorus, and age as parameters. The results are presented in Table 3.

### Table 3 Multivariate analysis of factors associated with 30-day mortality

| Parameter      | Value | P-value | Adjusted OR | 95 % CI Lower | 95 % CI Upper |
|----------------|-------|---------|-------------|---------------|---------------|
| CURB-65        | ≤1    | .000    | Ref.        |               |               |
|                | 2     | .017    | 1.4         | 1.1           | 1.9           |
|                | ≥3    | .000    | 3.5         | 2.6           | 4.7           |
| Albumin (g/dL) | <2    | .000    | Ref.        |               |               |
|                | >2    | .000    | 1.6         | 1.3           | 1.9           |
| RDW (%)        | >15   | .000    | 3.1         | 2.0           | 4.9           |
| Sodium (mmol/L)| ≥150  | .000    | 1.6         | 1.3           | 2.0           |
| Age (years)    | ≥80   | .000    | 2.1         | 1.6           | 6.8           |

Abbreviations: OR Odds Ratio, CI Confidence Interval, Ref. Reference, RDW Red Blood Cell Distribution Width

We also performed a Spearman’s Rank Correlation coefficient analysis to determine the relationship between serum phosphorus levels and various clinical parameters. The results are presented in Table 4.

### Table 4 Spearman’s Rank Correlation coefficient parameters

| Parameter      | % of Pts with P ≤ 1.5 | % of Pts with P 1.5-2.49 | % of Pts with P 2.5-3.99 | % of Pts with P 4-4.49 | % of Pts with P ≥ 4.5 | SPEARMAN |
|----------------|-----------------------|--------------------------|--------------------------|------------------------|------------------------|----------|
| Age (years)    | <40                   | 271                      | 4                        | 20                     | 62                     | 7        | 7        | 0.078 |
|                | 40-49                 | 209                      | 2                        | 15                     | 65                     | 11       | 11       |
|                | 50-59                 | 356                      | 1                        | 21                     | 58                     | 8        | 11       |
|                | 60-69                 | 579                      | 1                        | 16                     | 62                     | 9        | 11       |
|                | 70-79                 | 1016                     | 1                        | 15                     | 62                     | 9        | 13       |
|                | ≥80                   | 1445                     | 2                        | 12                     | 64                     | 10       | 12       |
| Albumin (g/dL) | <2                   | 513                      | 0                        | 12                     | 65                     | 11       | 12       | 0.040 |
|                | 2-3                   | 347                      | 4                        | 17                     | 50                     | 10       | 18       |
|                | 3-3.4                 | 1668                     | 1                        | 15                     | 62                     | 8        | 12       |
|                | Missing               | 721                      | 1                        | 14                     | 66                     | 10       | 9        |
| Sodium (mmol/L)| ≤130                 | 412                      | 2                        | 19                     | 61                     | 7        | 12       | 0.049 |
|                | 130-150               | 3366                     | 2                        | 15                     | 63                     | 10       | 11       |
|                | ≥150                  | 97                       | 1                        | 12                     | 55                     | 13       | 19       |
|                | Missing               | 627                      | 2                        | 17                     | 64                     | 10       | 8        |
| RDW (%)        | ≤15                   | 1958                     | 2                        | 17                     | 65                     | 8        | 8        | 0.144 |
|                | >15                   | 1373                     | 1                        | 11                     | 59                     | 11       | 17       |
|                | Missing               | 545                      | 2                        | 17                     | 64                     | 10       | 7        |
| CURB-65        | 0                     | 589                      | 1                        | 20                     | 66                     | 8        | 6        |
|                | 1                     | 881                      | 2                        | 16                     | 67                     | 8        | 6        |
|                | 2                     | 1286                     | 1                        | 13                     | 64                     | 10       | 12       |
|                | 3                     | 1120                     | 2                        | 13                     | 56                     | 11       | 18       |

Abbreviations: RDW Red Blood Cell Distribution Width
mortality was related to renal failure. We reexamined the association between serum phosphorus levels and 30-day mortality after adjustment for GFR levels. As shown in Fig. 2, even after adjustment for GFR levels, serum phosphorus levels below 1.5 mg/dl and levels above 4 mg/dl were associated with increased 30-day mortality at each GFR subgroup. This indicates that serum phosphorus levels were associated with 30-day mortality regardless of GFR, creatinine or urea levels.

We also adjusted for CURB-65 score to evaluate whether serum phosphorus levels have an additional prognostic value. We showed that the prognostic value of serum phosphorus levels below 1.5 mg/dl and levels above 4 mg/dl was maintained at each CURB-65 score. Therefore, in levels below 1.5 mg/dl, intravenous treatment of elemental phosphorus should be strongly considered.

In this study we reproduced our previous findings showing the elevated RDW is associated with increased mortality in patients with Community acquired pneumonia [26].

Our study has several limitations. The first is the retrospective design of the study. Secondly, data regarding the exact cause of 30-day mortality was not available in all cases and unfortunately, chest radiography appearance on admission was not included among the parameters examined. The third limitation was that not all patients admitted with CAP had serum phosphorus levels within 24 hours from admission. This may, in fact, reflect the fact that serum phosphorus levels were available for the more severe patients. This fact is consistent with our finding that the predictive value of serum phosphorus levels was greater in higher CURB-65 scores. Because of the retrospective nature of the study, data regarding vitamin D levels, Parathyroid hormone, Fibroblast growth factor-23 (FGF-23) levels and the urinary phosphorus excretion were not available. These vitamins and hormones are known to play a central role in the hemostasis of serum phosphorus, and might subsequently affect 30-day mortality. A fourth limitation was the lack exact information about antibiotic treatment pre admission; therefore, unfortunately, these patients were excluded.

Conclusions
Abnormal serum phosphorus levels on admission are associated with increased 30-mortality rates among adult patients hospitalized with CAP. The predictive value of phosphorus levels is maintained even after adjustment to GFR and CURB-65 levels. We believe there is a real need to examine the prognostic predictive value of serum phosphorus levels on admission on 30-day mortality in patients with community acquired pneumonia prospectively, along with vitamin D levels, Parathyroid hormone, Fibroblast growth factor-23 (FGF-23) levels and the urinary phosphorus excretion.

Abbreviations
CAP: Community-acquired pneumonia; OR: Odds ratio; CI: Confidence interval; RDW: Red blood cell distribution width; GFR: Glomerular filtration rate; BUN: Blood urea nitrogen.

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

Authors’ contributions
MEN had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. MM took part in data acquisition and the writing of the manuscript. MA took part in data acquisition and the writing of the manuscript. NA took part in data acquisition and the revising of the manuscript. ZSA contributed substantially to the study design, data analysis and interpretation, and the revising of the manuscript. EB had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. All authors read and approved the final manuscript.

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