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【 ORIGINAL ARTICLE 】

Significance of Hypophosphatemia in Patients with Pneumonia

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Abstract:

Objective Phosphate is a fundamental element involved in a number of physiological pathways. A previous study showed abnormal laboratory findings and a higher mortality in hypophosphatemic patients than in normophosphatemic patients with pneumonia. Sporadic cases of pneumonia due to *Legionella* spp., *Streptococcus pneumoniae*, and viruses have been reported; however, the significance of hypophosphatemia in patients with pneumonia has not been adequately studied. We determined whether or not hypophosphatemia in patients with community-acquired pneumonia (CAP) was associated with specific pathogens, patient factors, disease severity, and mortality.

Method We retrospectively analyzed 600 patients with CAP who were admitted to our hospital between January 1, 2010, and December 31, 2019.

Results Hypophosphatemia was found in 72 (12.0%) of the 600 patients. The most frequent causative microbial agents of CAP in patients with hypophosphatemia were *S. pneumoniae*, *Legionella* spp., and influenza virus, whereas in severely ill patients with hypophosphatemia, influenza virus was the most common. *Legionella* spp., diabetes mellitus, and severe pneumonia were the independent factors for hypophosphatemia in the multivariable analysis. An impaired performance status, severe status on admission, interstitial pneumonia, bacteremia, and guideline-discordant therapy were the independent factors associated with mortality in the multivariable analysis. Hypophosphatemia was not significantly associated with mortality but showed a trend towards higher mortality in the multivariable analysis.

Conclusion Hypophosphatemia was not associated with the prognosis in patients with CAP. However, the significance of hypophosphatemia for clinicians lies in the laboratory findings that predict abnormal glucose metabolism, *Legionella* infection, and severe disease.

Key words: pneumonia, hypophosphatemia, *Legionella*, severity, outcome

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Introduction

Phosphate is a fundamental element involved in numerous physiological pathways, such as skeletal development and mineralization, membrane composition, nucleotide structure, cellular signaling, energy storage and transfer, and maintenance of acid-base equilibrium (1). Because of its importance, phosphate homeostasis is closely regulated and maintained by a dynamic balance between urinary phosphate losses and net phosphate absorption from the gastrointestinal tract, with equal amounts deposited and reabsorbed from bone (2, 3). There are three primary mechanisms underlying hypophosphatemia: increased renal excretion, decreased intestinal absorption, and the movement of phosphate from extracellular to intracellular compartments.

Although hypophosphatemia is infrequent in the general population, it is encountered in general hospitalized patients

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(range, 2.2-3.1%), patients admitted to intensive-care units (28.8-34%), and those with infections, regardless of sepsis (65-80%) (2). Even though pneumonia accounts for a major proportion of hospitalized patients with infection and hypophosphatemia (2), the significance of hypophosphatemia in patients with pneumonia has not been sufficiently investigated.

Some sporadic cases of pneumonia due to *Legionella* spp. (4), *Streptococcus pneumoniae* (5), and viruses (6, 7), which are major pathogens of severe pneumonia (8), have been reported; however, whether hypophosphatemia reflects a severe condition of these patients or predicts infection by specific pathogens remains unclear.

We therefore examined whether or not hypophosphatemia in patients with pneumonia is associated with specific causative organisms, patient factors, disease severity, and mortality.

Materials and Methods

We conducted a retrospective study of all patients hospitalized with community-acquired pneumonia (CAP) over a 10-year period from January 2009 through December 2018 at our institution in Saitama, Japan. Pneumonia was diagnosed based on symptoms suggestive of lower respiratory tract infections and the development of infiltrations on chest X-ray. The excluded patients comprised those with hospital-acquired pneumonia (9), those showing immunosuppression [acquired immunodeficiency syndrome (AIDS) or receiving chemotherapy for malignancy], and those with tuberculosis, non-resected lung cancer, or a confirmed alternative diagnosis lasting until the end of the follow-up period.

The diagnosis of causative microorganisms was based on the results of semi-quantitative cultures of respiratory samples or blood, paired sera, urinary antigen tests for *S. pneumoniae* and *Legionella pneumophila*, and nasopharyngeal swabs for influenza virus, as reported previously (8). The causative microorganisms for which paired-sera were used in the diagnosis were *M. pneumoniae*, *Legionella* spp., *Chlamydophila pneumoniae*, *C. psittaci*, adenovirus, respiratory syncytial virus, influenza virus, and human parainfluenza viruses 1, 2, 3, and 4. In addition, viral infection was diagnosed when real-time polymerase chain reaction (PCR) was positive.

Respiratory specimens obtained from bronchoalveolar lavage fluid, pharyngeal swab, or sputum were transported on dry ice, stored at -70 °C, and used for the detection of respiratory pathogens on a Rotor-Gene Q instrument (Qiagen, Hilden, Germany) with multiplex reverse-transcription PCR (RT-PCR) using an FTD Resp 21 Kit (Fast Track Diagnostics, Silema, Malta). The kit detects the following respiratory pathogens: influenza A and B viruses; coronaviruses NL63, 229E, OC43, and HKU1; human parainfluenza viruses 1, 2, 3, and 4; human metapneumovirus A/B; rhinovirus; respiratory syncytial virus A/B; adenovirus; enterovirus; human parechovirus; bocavirus; and *Mycoplasma pneumoniae*. An EZ1 Virus Mini Kit v2.0 was used for nucleic acid extraction (Qiagen). A threshold cycle value of <33 was considered to be a positive result on RT-PCR, as indicated in the manufacturer's instructions.

Disease severity on admission was based on the criteria of the American Thoracic Society/Infectious Disease Society of America (IDSA/ATS) guidelines (9). Severe disease was diagnosed when at least one major criterion or three minor criteria of the guidelines were present. Hypophosphatemia was defined as a serum phosphorus level <2.0 mg/dL on admission. Diabetes mellitus was defined if the patient was previously diagnosed as having the condition and was currently being treated with insulin or oral hypoglycemic agents or had a high serum glucose concentration or high HbA1c levels during hospitalization, according to the Japanese Diagnostic Criteria of Diabetes Mellitus (10).

Rhabdomyolysis was defined as a creatine kinase level of >1,000 IU/L (11). The performance status (PS) was recorded on admission based on anamnesis from the patients and the patients' families and classified based on the criteria suggested by the Eastern Cooperative Oncology Group (ECOG) (12). The definition of healthcare contact was based on the healthcare-associated pneumonia criteria suggested by the ATS/IDSA (13). Patients' comorbidities and laboratory data were searched in their medical records through manual searching and the use of the hospital information system.

The treatment prescribed during the first 24 hours of hospitalization was considered the initial treatment. The initial antibiotic regimen was defined as being concordant when the antibiotics chosen by the attending physician were in accordance with the recommendations of the 2019 IDSA/ATS guidelines (9), regardless of any additionally administered antibiotics.

The following variables were assessed as possible risk factors for the severity on admission and in-hospital mortality of pneumonia: age, male sex, smoking habit, presence of comorbid illnesses, history of healthcare contact, the history of prior antibiotics administered by a local physician, the presence of rhabdomyolysis and hypophosphatemia, and causative pathogens. Concordance of the initial antibiotic therapy with the ATS/IDSA guidelines (9) was also assessed as a possible risk factor for in-hospital mortality.

The study protocol was approved by the Ethical Committee of the Saitama Cardiovascular and Respiratory Center. This same committee approved the verbal consent procedure. We used an opt-out method for patient inclusion and disclosed this to the hospitalized patients. No patients refused to participate.

Statistical analyses

The results are presented as numbers and percentages or mean±standard deviation unless otherwise indicated. Comparisons of patients with and without hypophosphatemia were performed using Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. Risk factors for hypophosphatemia and in-hospital mortality were

Table 1. Patient Characteristics.

Characteristic	Total (n=600)	Hypophosphatemia (n=72)	Non-hypophosphatemia (n=528)	p value
Female sex	175 (29.2%)	17 (23.6%)	158 (29.9%)	0.333
Age (years)	67.9±15.2	69.7±14.1	67.6±15.3	0.265
<65	184 (30.7%)	18 (25.0%)	166 (31.4%)	0.485
65-74	200 (33.3%)	23 (31.9%)	177 (33.5%)	
75-89	204 (34.0%)	29 (40.3%)	175 (33.1%)	
90-	12 (2.0%)	2 (2.8%)	10 (1.9%)	
Pathogen identified	304 (50.7%)	39 (54.2%)	265 (50.2%)	0.533
Comorbidity				
Pulmonary disease	321 (53.5%)	38 (52.8%)	283 (53.6%)	0.901
Non-pulmonary disease	312 (52.0%)	47 (65.3%)	265 (50.2%)	0.017
Smoking history	391 (65.2%)	50 (69.4%)	341 (64.6%)	0.510
CAP/HCAP				
CAP without health care contacts	401 (66.8%)	52 (72.2%)	349 (66.1%)	0.224
CAP with health care contacts	191 (31.8%)	18 (25.0%)	173 (32.8%)	
Performance status				
0	352 (58.7%)	45 (62.5%)	307 (58.1%)	0.637
1-2	218 (36.3%)	23 (31.9%)	195 (36.9%)	
3-4	28 (4.7%)	4 (5.6%)	24 (4.5%)	
Disease severity on admission				
Severe	75 (12.5%)	19 (26.4%)	56 (10.6%)	<0.001
In-hospital mortality	22 (3.7%)	5 (6.9%)	17 (3.2%)	0.168

CAP: community-acquired pneumonia, HCAP: healthcare-associated pneumonia

evaluated by univariable and multivariable logistic regression analyses. The results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

We carefully selected factors considered in the multivariable logistic model by adopting five strategies. First, we forced clinically meaningful factors evaluated in each multivariable logistic model based on expert knowledge, despite the statistical results of factors in the univariable logistic model. Second, factors consisting of more than two categories, namely age and performance status, were simplified by reducing the number of categories to increase precision of the model estimates. Third, factors that were missing in many of the patients or those suspected of causing collinearity were not eliminated. No imputation was made for missing data. Fourth, the number of events and the Hosmer-Lemeshow goodness of fit (14) were considered to select the number of factors included in the multivariable logistic model. Fifth, Firth's bias correction was used to compensate for the small number of events (15).

A p value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed with the SAS software program, version 9.4 (SAS Institute, Cary, USA).

Results

Patient characteristics

We included 600 patients in the present study. The baseline characteristics of the study patients are shown in Table 1. Regarding disease severity on admission, 75 (12.5%) of the patients were classified as having severe pneumonia, and 22 (3.7%) died during their hospital stay. Hypophosphatemia was found in 72 (12.0%) of the 600 patients and was present in 19 (26.4%) of the severely ill patients and in 5 (6.9%) of the patients who died. Three patients had severe hypophosphatemia (<1.0 mg/dL), of whom 1 was severely ill and died, although the other 2 did not. The frequency of non-pulmonary disease and the proportion of severe cases were significantly higher in the patients with hypophosphatemia than in those without it. Interventions for hypophosphatemia were not performed in any of the patients. Among the 72 patients with hypophosphatemia, serum phosphorus levels were not measured in 38 patients after treatment. In the other 34 patients, the serum phosphorus levels improved to >2.0 mg/dL during their subsequent treatment course.

Microbiological etiology of pneumonia in patients with and without hypophosphatemia

The diagnostic methods used and the results obtained are listed in Table 2. The use of RT-PCR was begun from 2016 and not performed in cases before that. Furthermore, it was not used in every case from 2016 onward.

Pathogens were identified in 39 (54.2%) of the hypophosphatemia patients and 265 (50.2%) of the non-hypophosphatemia patients (Table 1). Polymicrobial infections were identified in 9 (12.5%) of the hypophosphatemia patients and 44 (8.3%) of the non-hypophosphatemia patients (Table 3). The 4 most frequently isolated pathogens in

Table 2. Diagnostic Methods and Patient Results (n=600).

Method	No. of episodes studied	No. of positive diagnostic studies(%)
Paired sera	514	115 (22.4%)
Rapid influenza diagnostic test	591	32 (5.4%)
RT-PCR	52	27 (51.9%)
Urinary antigen		
Streptococcus pneumoniae	588	104 (17.7%)
Legionella sp.	588	16 (2.7%)
Culture		
Sputum	534	101 (18.9%)
Transbronchial aspirate	30	8 (26.7%)
Protected specimen brush	3	1 (33.3%)
Bronchial washing	12	4 (33.3%)
Bronchoalveolar lavage fluid	39	11 (28.2%)
Blood	493	16 (3.2%)
Pleural fluid	13	1 (7.7%)

RT-PCR: reverse-transcription polymerase chain reaction

the hypophosphatemia patients were *S. pneumoniae* (19.4%), *Legionella* spp. and influenza virus (11.1% each), and a virus other than influenza virus (6.9%). In contrast, the 5 most frequently isolated pathogens in the non-hypophosphatemia patients were *S. pneumoniae* (18.6%), influenza virus (11.7%), *M. pneumoniae* (6.3%), *C. pneumoniae* (5.3%), and *Legionella* spp. (3.6%) (Table 3). *Legionella* spp. were identified as etiologies significantly more frequently in the hypophosphatemia patients than in the non-hypophosphatemia patients (11.1% vs. 3.6%, p=0.010). The 3 most frequently isolated pathogens in the hypophosphatemia patients with severe pneumoniae were influenza virus (26.3%), *S. pneumoniae* (21.0%), and *Legionella* spp. (15.8%).

Factors contributing to hypophosphatemia

The results of univariable and multivariable logistic regression analyses for hypophosphatemia are provided in Table 4. Univariable analyses showed that *Legionella* spp. (OR, 3.44; 95% CI, 1.46 to 8.14; p=0.005), chronic non-pulmonary diseases (OR, 1.85; 95% CI, 1.11 to 3.08; p= 0.019), diabetes mellitus (OR, 2.72; 95% CI, 1.53 to 4.82; p <0.001), arrhythmia (OR, 2.21; 95% CI, 1.02 to 4.80; p= 0.044), rhabdomyolysis (OR, 6.51; 95% CI, 2.48 to 17.08; p <0.001), C-reactive protein (CRP) (OR, 1.06; 95% CI, 1.03 to 1.08; p<0.001), and disease severity on admission (OR, 3.05; 95% CI, 1.69 to 5.50; p<0.001) were independent factors for hypophosphatemia. Next, multivariable analyses showed that *Legionella* spp. (OR, 2.89; 95% CI, 1.19 to 6.99; p=0.019), diabetes mellitus (OR, 2.53; 95% CI, 1.41 to 4.56; p=0.002), and severe pneumonia (OR, 2.86; 95% CI, 1.57 to 5.22; p=0.001) were independent factors for hypophosphatemia.

In the 398 cases in which serum glucose and phosphorus were measured simultaneously, we created a scatter plot of blood glucose and phosphorus levels (Figure). The Pearson's product rate correlation coefficient was -0.098.

The subspecies of *Legionella* in the cases of pneumonia with hypophosphatemia were *L. pneumophila* serogroup 1 in two cases, *L. pneumophila* serogroup 2 in one case, *L. longbeachae* in no cases, and unknown in five cases. The subspecies in the cases without hypophosphatemia were *L. pneumophila* serogroup 1 in 5 cases, *L. pneumophila* serogroup 2 in 0 cases, *L. longbeachae* in 1 case, and unknown in 13 cases.

Risk factors for mortality

The results of the univariable and multivariable logistic regression analyses for morality are given in Table 5. Univariable analyses showed that advanced age (≥65 years old) (OR, 3.77; 95% CI, 1.00 to 14.24; p=0.050), interstitial pneumonia (OR, 3.15; 95% CI, 1.15 to 8.62; p=0.025), hypertension (OR, 2.76; 95% CI, 1.12 to 6.81; p=0.028), long-term oxygen therapy (OR, 3.72; 95% CI, 1.24 to 11.14; p= 0.019), PS (ECOG 3-4) (OR, 7.40; 95% CI, 2.57 to 21.32; p<0.001), rhabdomyolysis (OR, 6.53; 95% CI, 1.82 to 23.34; p=0.004), blood urea nitrogen (≥20 mg/dL) (OR, 4.65; 95% CI, 1.95 to 11.07; p<0.001), procalcitonin (OR, 1.06; 95% CI, 1.01 to 1.12; p=0.016), CRP (OR, 1.06; 95% CI, 1.02 to 1.09; p=0.002), bacteremia (OR, 21.33; 95% CI, 6.95 to 65.44; p<0.001), disease severity on admission (OR, 11.74; 95% CI, 4.90 to 28.13; p<0.001), and concordance with guideline-recommended treatment (i.e., discordant therapy) (OR, 3.15; 95% CI, 1.15 to 8.62; p=0.025) were independent factors. Next, multivariable analyses revealed that interstitial pneumonia (OR, 7.06; 95% CI, 2.12 to 23.46; p= 0.001), PS (ECOG 3-4) (OR, 11.48; 95% CI, 3.32 to 39.72; p<0.001), bacteremia (OR, 11.80; 95% CI, 2.77 to 50.18; p =0.001), disease severity on admission (OR, 7.11; 95% CI, 2.53 to 20.01; p<0.001), and discordant therapy (OR, 4.46; 95% CI, 1.38 to 14.36; p=0.012) were independent factors associated with mortality.

Table 3. Etiology of Pneumonia in the Hypophosphatemia and Non-hypophosphatemia Patients.

	Total	Hypophosphatemia	Non-hypophosphatemia	p value
	(n=600)	(n=72)	(n=528)	
Streptococcus pneumoniae	112 (18.7%)	14 (19.4%)	98 (18.6%)	0.872
Influenza virus	70 (11.7%)	8 (11.1%)	62 (11.7%)	1.000
Mycoplasma pneumoniae	36 (6.0%)	3 (4.2%)	33 (6.3%)	0.606
Legionella spp.	27 (4.5%)	8 (11.1%)	19 (3.6%)	0.010
Pseudomonas aeruginosa	13 (2.2%)	2 (2.8%)	11 (2.1%)	0.662
Haemophilus influenzae	13 (2.2%)	2 (2.8%)	11 (2.1%)	0.662
GNEB	14 (2.3%)	3 (4.2%)	11 (2.1%)	0.230
Chlamydophila pneumoniae	30 (5.0%)	2 (2.8%)	28 (5.3%)	0.563
Chlamydophila psittaci	2 (0.3%)	0 (0.0%)	2 (0.4%)	1.000
Moraxella catarrhalis	6 (1.0%)	0 (0.0%)	6 (1.1%)	1.000
Streptococcus spp. [a]	4 (0.7%)	0 (0.0%)	4 (0.8%)	1.000
MSSA	6 (1.0%)	1 (1.4%)	5 (0.9%)	0.537
Acinetobacter	1 (0.2%)	0 (0.0%)	1 (0.2%)	1.000
Other bacteria [b]	6 (1.0%)	1 (1.4%)	5 (1.7%)	0.537
Virus (other than Influenza virus)	20 (3.3%)	5 (6.9%)	15 (2.8%)	0.079
Polymicrobial infection [c]	53 (8.8%)	9 (12.5%)	44 (8.3%)	0.266
Unknown	294 (49.0%)	33 (45.8%)	261 (49.4%)	0.616

This number includes not only monomicrobial but also polymicrobial infection.

[a] *Streptococcus* sp. means other than *S. pneumoniae*. [b] "Other bacteria" includes *Staphylococcus haemolyticus* (n=1) in the hypophosphatemia patients, and *Haemophilus parainfluenzae* (n=2), *Citrobacter freundii*, *Achromobacter xylosoxidans*, *Rothia mucilaginosa* (n=1 each) in the non-hypophosphatemia patients. [c] "Polymicrobial infection" includes *S. pneumoniae*+influenza virus, *C. pneumoniae*+*Legionella* spp., *C. pneumoniae*+influenza virus, GNEB+influenza virus, human parainfluenza virus 3+respiratory syncytial virus, *S. pneumoniae*+influenza virus+*Staphylococcus haemolyticus*, *S. pneumoniae*+adenovirus+coronaviruses 229E, *Legionella* spp. +rhinovirus+coronavirus 229E, *Legionella* spp. +influenza virus+rhinovirus+human parainfluenza virus 2+parechovirus (n=1 each) in the hypophosphatemia patients, and *S. pneumoniae* +influenza virus (n=15), *S. pneumoniae*+*C. pneumoniae* (n=5), *S. pneumoniae*+MSSA, *S. pneumoniae*+GNEB, *S. pneumoniae*+rhinovirus, *M. pneumoniae*+*P. aeruginosa*, *M. pneumoniae*+*S. agalactiae*, *M. pneumoniae*+influenza virus, *C. pneumoniae*+influenza virus, *C. pneumoniae*+*Rothia mucilaginosa*, *Legionella* spp. +*H. influenzae*, *Legionella* spp. +*M. catarrhalis*, *Legionella* spp. +influenza virus, MSSA+GNEB, MSSA+influenza virus, *C. psittaci*+human parainfluenza virus 1, rhinovirus+parechovirus, *S. pneumoniae*+*C. pneumoniae*+influenza virus, *S. pneumoniae*+*C. pneumoniae*+*M. catarrhalis*, *C. pneumoniae*+*P. aeruginosa*+GNEB, MSSA+GNEB+influenza virus, influenza virus+rhinovirus+coronavirus 229E, rhinovirus+parechovirus+human parainfluenza virus 2, respiratory syncytial virus+human parainfluenza virus 1+parechovirus, respiratory syncytial virus+human parainfluenza virus 1+coronavirus 229E, rhinovirus+human parainfluenza virus 2+coronavirus NL63+human metapneumovirus (n=1 each) in the non-hypophosphatemia patients. GNEB: Gram-negative enteric bacilli, MSSA: methicillin-susceptible *Staphylococcus aureus*

Discussion

The most frequently isolated pathogen in the hypophosphatemia patients was *S. pneumoniae*, followed by *Legionella* spp. and influenza virus. In severe cases, however, influenza virus was the most common. *Legionella* spp., diabetes mellitus, and severe pneumonia were independent factors for hypophosphatemia in the multivariable analysis. Impaired PS, disease severity, interstitial pneumonia, bacteremia, and concordance with guideline-recommended treatment (i.e. discordant therapy) were independent factors associated with mortality in the multivariable analysis. Hypophosphatemia was not significantly associated with mortality but showed a trend towards an increased mortality.

Several different pathogens have been reported in patients with hypophosphatemia associated with pneumonia (4-7). In the present study, *Legionella* spp. was the only pathogen associated with hypophosphatemia, independent of the other factors in the patients with pneumonia. The main mechanism of hypophosphatemia in *Legionella* pneumonia is speculated to be increased renal phosphate excretion (4), and the following three sub-mechanisms have been suggested (16): rhabdomyolysis- and myoglobinuria-induced tubular injury, direct *Legionella* infection in the renal tubules, and a complication of acute tubulointerstitial nephritis. *Legionella* spp. are pathogens that account for 1-8% of pneumonias and often causes severe pneumonia (17-19). Therefore, *Legionella* pneumonia needs to be diagnosed and treated promptly with appropriate antibiotics. A urinary antigen test is used for the rapid diagnosis of *Legionella*, but it is important to predict *Legionella* pneumonia because the sensitivity of this test is not sufficient. Multiple scoring systems have been proposed to predict *Legionella* spp. as pathogens of pneumonia (20-23). Among them, however, only one scoring system includes hypophosphatemia (22).

Table 4. Logistic Regression Analysis of the Risk of Hypophosphatemia in the Study Patients.

		n	Hypophosphatemia (%)	Univariable model		Multivariable model	
				OR (95% CI)	p value	OR (95% CI)	p value
Sex	Male	425	55 (12.9%)	1.36 (0.77, 2.40)	0.294		
Age (years)	90-	12	2 (16.7%)	2.14 (0.47, 9.74)	0.324		
	75-89	204	29 (14.2%)	1.51 (0.81, 2.81)	0.191		
	65-74	200	23 (11.5%)	1.19 (0.62, 2.27)	0.595		
	<65	184	18 (9.8%)	1			
Vaccination history							
23-valent pneumococcal polysaccharide	Unknown	15	4 (26.7%)	3.10 (0.80, 12.10)	0.103		
vaccination within 5 years	No	519	61 (11.8%)	1.06 (0.47, 2.39)	0.880		
Influenza vaccination within one year	Unknown	220	23 (10.5%)	0.70 (0.36, 1.34)	0.282		
	No	254	31 (12.2%)	0.83 (0.44, 1.54)	0.547		
Prior antibiotic treatment	No	363	47 (12.9%)	1.23 (0.73, 2.05)	0.434		
Identified pathogen	Yes	304	39 (12.8%)	1.17 (0.72, 1.91)	0.531		
Unidentified pathogen	Yes	294	33 (11.2%)	0.87 (0.53, 1.42)	0.571		
Streptococcus pneumoniae	Yes	112	14 (12.5%)	1.08 (0.58, 2.01)	0.800		
Legionella spp.	Yes	27	8 (29.6%)	3.44 (1.46, 8.14)	0.005	2.89 (1.19, 6.99)	0.019
Influenza virus	Yes	70	8 (11.4%)	0.98 (0.46, 2.12)	0.966		
Virus (other than influenza virus)	Yes	20	5 (25.0%)	2.70 (0.96, 7.55)	0.059		
Polymicrobial infection	Yes	53	9 (17.0%)	1.63 (0.77, 3.46)	0.205		
Comorbidities							
Chronic pulmonary diseases	Yes	321	38 (11.8%)	0.97 (0.59, 1.58)	0.891		
COPD	Yes	158	14 (8.9%)	0.66 (0.36, 1.21)	0.180		
Asthma	Yes	56	10 (17.9%)	1.74 (0.84, 3.60)	0.133		
Bronchiectasis	Yes	32	4 (12.5%)	1.15 (0.41, 3.27)	0.788		
Pulmonary NTM	Yes	37	6 (16.2%)	1.54 (0.63, 3.77)	0.341		
Old tuberculosis	Yes	21	3 (14.3%)	1.39 (0.42, 4.60)	0.590		
Chronic pulmonary aspergillosis	Yes	9	0 (0.0%)	0.38 (0.02, 7.63)	0.525		
Interstitial pneumonia	Yes	57	5 (8.8%)	0.74 (0.29, 1.86)	0.521		
Lung cancer surgery	Yes	16	3 (18.8%)	1.92 (0.56, 6.62)	0.301		
Pneumoconiosis	Yes	2	0 (0.0%)	1.45 (0.03, 60.37)	0.845		
Chronic empyema	Yes	2	0 (0.0%)	1.45 (0.03, 60.37)	0.845		
Chronic non-pulmonary diseases	Yes	312	47 (15.1%)	1.85 (1.11, 3.08)	0.019		
Hypertension	Yes	93	13 (14.0%)	1.26 (0.67, 2.40)	0.473		
Congestive heart failure	Yes	24	5 (20.8%)	2.13 (0.78, 5.78)	0.138		
Ischemic heart diseases	Yes	24	5 (20.8%)	2.13 (0.78, 5.78)	0.138		
Diabetes mellitus	Yes	86	20 (23.3%)	2.72 (1.53, 4.82)	<0.001	2.53 (1.41, 4.56)	0.002
Valvular disease	Yes	9	1 (11.1%)	1.29 (0.20, 8.14)	0.790		
Arrhythmia	Yes	42	9 (21.4%)	2.21 (1.02, 4.80)	0.044		
Cardiomyopathy	Yes	5	0 (0.0%)	0.66 (0.03, 15.80)	0.795		
Neurological disorders	Yes	29	4 (13.8%)	1.30 (0.45, 3.71)	0.627		
Post surgery of upper digestive system	Yes	12	3 (25.0%)	2.75 (0.75, 10.11)	0.127		
Chronic liver diseases	Yes	12	3 (25.0%)	2.75 (0.75, 10.11)	0.127		
Connective tissue diseases	Yes	34	2 (5.9%)	0.54 (0.14, 2.05)	0.366		
Primary immunodeficiency disease	Yes	1	0 (0.0%)	2.42 (0.03, 225.72)	0.703		
Immunosuppression due to systemic corticosteroids or immunosuppressants	Yes	41	4 (9.8%)	0.86 (0.31, 2.39)	0.774		
Psychiatric disorders	Yes	13	3 (23.1%)	2.49 (0.69, 8.94)	0.163		
Malignancy	Yes	16	2 (12.5%)	1.26 (0.31, 5.13)	0.749		
Alcoholism	Yes	3	0 (0.0%)	1.04 (0.03, 31.97)	0.983		
CKD	Yes	7	1 (14.3%)	1.69 (0.25, 11.43)	0.593		
Smoking history	Yes	391	50 (12.8%)	1.23 (0.73, 2.09)	0.439		
Long-term oxygen therapy	Yes	39	2 (5.1%)	0.46 (0.12, 1.74)	0.255		
CAP/HCAP	HCAP	191	18 (9.4%)	0.71 (0.40, 1.24)	0.232		
Performance status	Unknown	0	0 (-%)				
	3-4	28	4 (14.3%)	1.24 (0.43, 3.62)	0.692		
	1-2	218	23 (10.6%)	0.81 (0.48, 1.38)	0.442		
	0	352	45 (12.8%)	1			
Rhabdomyolysis	Yes	18	8 (44.4%)	6.51 (2.48, 17.08)	<0.001		
Blood urea nitrogen ≥20 mg/dL	Yes	169	23 (13.6%)	1.24 (0.73, 2.10)	0.425		
Procalcitonin		161		1.04 (1.00, 1.08)	0.080		
C-reactive protein		600		1.06 (1.03, 1.08)	<0.001		
Bacteremia	Yes	16	2 (12.5%)	1.26 (0.31, 5.13)	0.749		
Disease severity on admission	Severe	75	19 (25.3%)	3.05 (1.69, 5.50)	<0.001	2.86 (1.57, 5.22)	0.001
Concordance with CAP guideline-recommended treatment regimen	Discordant	57	4 (7.0%)	0.58 (0.21, 1.59)	0.293		
	Concordant	543	68 (12.5%)	1			
Number of antibiotics	Monotherapy	108	7 (6.5%)	0.48 (0.22, 1.06)	0.070		
	≥2 drugs	492	65 (13.2%)	1			

Values represent p value for category against the reference. CAP: community-acquired pneumonia, CI: confidence interval, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, HCAP: healthcare-associated pneumonia, NTM: nontuberculous mycobacteriosis, OR: odds ratio

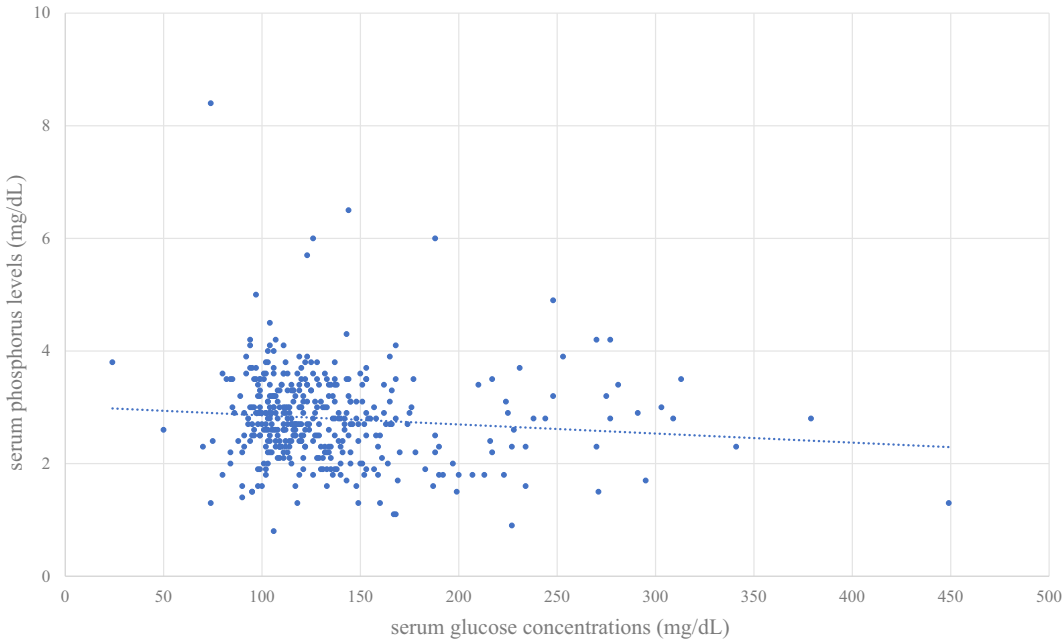

Figure. Scatter plot of serum glucose and phosphorus levels in the 398 cases in which the levels were measured simultaneously. The Pearson's product rate correlation coefficient was -0.098.

Our study suggested that hypophosphatemia may be a laboratory finding that contributes to the prediction of *Legionella* pneumonia. It would be desirable to construct a highly accurate scoring system that includes hypophosphatemia. The relationship between *Legionella* subspecies and hypophosphatemia has not been reported before to our knowledge. Statistical analysis was not possible in this study because of the small number of cases, so further studies with a larger number of cases will be required in the future.

In the present study, diabetes mellitus was significantly associated with hypophosphatemia. Elevated serum glucose concentrations depolarize the transmembrane electrochemical Na+ gradient of the brush border membrane for inorganic phosphate entry into the tubular cells and decrease intracellular phosphate levels, leading to hyperphosphaturia (24, 25). A previous study showed that hypophosphatemic patients with CAP manifested higher levels of serum glucose (26), suggesting phosphorus metabolism in diabetic patients. However, stress hyperglycemia, defined as a transient increase in the blood glucose concentration during acute physiological illness, is observed in patients with CAP (27, 28). Hypophosphatemia may reflect the effects of hyperglycemia associated with pneumoniae itself as well as underlying diabetes mellitus. A previous study showed hyperglycemia to be associated with a poor outcome from CAP (29). Furthermore, another study reported that undiagnosed diabetes mellitus was prevalent among patients with CAP (27) and was associated with a poor 180-day survival rate. These findings suggest the importance of the prompt recognition of abnormal glucose metabolism in CAP when hypophosphatemia is observed in a patient with CAP. However, the Pearson's correlation coefficient was -0.098 in the scatter plot of plasma phosphorus and blood glucose levels in this study, suggesting that the plasma phosphorus level may be an independently important electrolyte because plasma phosphorus does not necessarily correlate with the blood glucose level measured at the same time.

Redistribution across the cell membrane is reported to be the most common cause of hypophosphatemia in severe cases (30). High levels of catecholamines in serum, stimulation of carbohydrate metabolism by the actions of blood glucose and insulin (31), and respiratory alkalosis (32) cause an intracellular shift of phosphorus in such patients. Hypophosphatemia appears early in severe cases and has been reported to be associated with mortality (33-35). A previous study showed a higher mortality in hypophosphatemic patients with pneumonia than in those with normophosphatemia (26). In the present study, hypophosphatemia was more common in severe cases and was not significantly associated with in-hospital mortality. In a previous retrospective study, severe hypophosphatemia (<1.0 mg/dL) was reported to be an independent predictor of mortality in sepsis (35). However, there were only three cases of severe hypophosphatemia in the present study. The degree of hypophosphatemia in patients with pneumonia may be related to the severity and prognosis of the disease, but the number of cases of severe hypophosphatemia was small, making it difficult to evaluate. Because the numbers of severely ill patients and deaths were limited in the present study, it will be necessary to increase the number of cases and study this further in the future. However, as hypophosphatemia was not significantly associated with the prognosis in the univariate analysis, it may be more important as a marker of metabolic disorders, severity, and specific pathogen infections than as a factor affecting the prognosis itself.

In the present study, 8 (44.4%) of the 18 patients with

Table 5. Logistic Regression Analysis of the Risk of In-hospital Mortality in the Study Patients.

		n	Non-survivors (%)	Univariable model		Multivariable model	
				OR (95% CI)	p value	OR (95% CI)	p value
Sex	Male	425	15 (3.5%)	0.85 (0.35, 2.07)	0.718		
Age (years)	65-	416	20 (4.8%)	3.77 (1.00, 14.24)	0.050	1.53 (0.37, 6.38)	0.558
	<65	184	2 (1.1%)	1		1	
Vaccination history							
23-valent pneumococcal polysaccharide	Unknown	15	1 (6.7%)	1.88 (0.24, 14.54)	0.546		
vaccination within 5 years	No	519	18 (3.5%)	0.67 (0.21, 2.18)	0.505		
Influenza vaccination within one year	Unknown	220	5 (2.3%)	0.90 (0.23, 3.52)	0.880		
	No	254	14 (5.5%)	2.13 (0.65, 7.00)	0.214		
Prior antibiotic treatment	No	363	17 (4.7%)	2.10 (0.79, 5.56)	0.136		
Identified pathogen	Yes	304	12 (3.9%)	1.17 (0.50, 2.70)	0.719		
Unidentified pathogen	Yes	294	9 (3.1%)	0.72 (0.31, 1.69)	0.454		
Streptococcus pneumoniae	Yes	112	5 (4.5%)	1.38 (0.52, 3.69)	0.522		
Legionella spp.	Yes	27	0 (0.0%)	0.45 (0.03, 7.93)	0.582		
Influenza virus	Yes	70	5 (7.1%)	2.46 (0.91, 6.68)	0.076		
Virus (other than influenza virus)	Yes	20	0 (0.0%)	0.60 (0.03, 11.07)	0.735		
Polymicrobial infection	Yes	53	3 (5.7%)	1.88 (0.58, 6.13)	0.297		
Comorbidities							
Chronic pulmonary diseases	Yes	321	15 (4.7%)	1.84 (0.76, 4.47)	0.180		
COPD	Yes	158	7 (4.4%)	1.37 (0.56, 3.34)	0.494		
Asthma	Yes	56	2 (3.6%)	1.17 (0.30, 4.54)	0.817		
Bronchiectasis	Yes	32	1 (3.1%)	1.21 (0.22, 6.76)	0.826		
Pulmonary NTM	Yes	37	3 (8.1%)	2.83 (0.85, 9.43)	0.090		
Old tuberculosis	Yes	21	1 (4.8%)	1.90 (0.33, 10.94)	0.473		
Chronic pulmonary aspergillosis	Yes	9	1 (11.1%)	4.68 (0.72, 30.68)	0.107		
Interstitial pneumonia	Yes	57	5 (8.8%)	3.15 (1.15, 8.62)	0.025	7.06 (2.12, 23.46)	0.001
Lung cancer surgery	Yes	16	1 (6.3%)	2.54 (0.43, 15.05)	0.305		
Pneumoconiosis	Yes	2	0 (0.0%)	5.13 (0.12, 216.23)	0.392		
Chronic empyema	Yes	2	0 (0.0%)	5.13 (0.12, 216.23)	0.392		
Chronic non-pulmonary diseases	Yes	312	15 (4.8%)	1.96 (0.80, 4.75)	0.139		
Hypertension	Yes	93	7 (7.5%)	2.76 (1.12, 6.81)	0.028		
Congestive heart failure	Yes	24	2 (8.3%)	3.02 (0.74, 12.29)	0.123		
Ischemic heart diseases	Yes	24	2 (8.3%)	3.02 (0.74, 12.29)	0.123		
Diabetes mellitus	Yes	86	2 (2.3%)	0.71 (0.19, 2.73)	0.622		
Valvular disease	Yes	9	0 (0.0%)	1.33 (0.06, 27.49)	0.852		
Arrhythmia	Yes	42	1 (2.4%)	0.90 (0.16, 4.97)	0.907		
Cardiomyopathy	Yes	5	0 (0.0%)	2.32 (0.09, 56.78)	0.606		
Neurological disorders	Yes	29	2 (6.9%)	2.44 (0.61, 9.80)	0.207		
Post surgery of upper digestive system	Yes	12	1 (8.3%)	3.44 (0.56, 21.31)	0.184		
Chronic liver diseases	Yes	12	0 (0.0%)	1.01 (0.05, 19.67)	0.996		
Connective tissue diseases	Yes	34	1 (2.9%)	1.14 (0.20, 6.31)	0.884		
Primary immunodeficiency disease	Yes	1	0 (0.0%)	8.43 (0.09, 807.94)	0.360		
Immunosuppression due to systemic corticosteroids or immunosuppressants	Yes	41	3 (7.3%)	2.52 (0.76, 8.33)	0.130		
Psychiatric disorders	Yes	13	1 (7.7%)	3.16 (0.52, 19.31)	0.212		
Malignancy	Yes	16	0 (0.0%)	0.76 (0.04, 14.20)	0.852		
Alcoholism	Yes	3	0 (0.0%)	3.65 (0.12, 114.85)	0.462		
CKD	Yes	7	0 (0.0%)	1.70 (0.08, 37.17)	0.738		
Smoking history	Yes	391	11 (2.8%)	0.52 (0.23, 1.20)	0.127		
Long-term oxygen therapy	Yes	39	4 (10.3%)	3.72 (1.24, 11.14)	0.019		
Healthcare contacts	Yes	191	11 (5.8%)	2.16 (0.94, 5.00)	0.071		
Performance status	Unknown	0	0 (-%)				
	3-4	28	5 (17.9%)	7.40 (2.57, 21.32)	<0.001	11.48 (3.32, 39.72)	<0.001
	0-2	570	17 (3.0%)	1		1	
Rhabdomyolysis	Yes	18	3 (16.7%)	6.53 (1.82, 23.34)	0.004	3.54 (0.70, 17.91)	0.126
Blood urea nitrogen (≥20 mg/dL)	Yes	169	14 (8.3%)	4.65 (1.95, 11.07)	<0.001		
Hypophosphatemia		72	5 (6.9%)	2.38 (0.88, 6.45)	0.088	2.28 (0.72, 7.27)	0.163
Procalcitonin		161		1.06 (1.01, 1.12)	0.016		
C-reactive protein	Yes	600		1.06 (1.02, 1.09)	0.002		
Bacteremia	Yes	16	6 (37.5%)	21.33 (6.95, 65.44)	<0.001	11.80 (2.77, 50.18)	0.001
Disease severity on admission	Severe	75	13 (17.3%)	11.74 (4.90, 28.13)	<0.001	7.11 (2.53, 20.01)	<0.001
Concordance with CAP guideline-recommended treatment regimen	Discordant	57	5 (8.8%)	3.15 (1.15, 8.62)	0.025	4.46 (1.38, 14.36)	0.012
	Concordant	543	17 (3.1%)	1		1	
Number of antibiotics	Monotherapy	108	6 (5.6%)	1.83 (0.72, 4.67)	0.205		
	≥2 drugs	492	16 (3.3%)	1			

Values represent p value for category against the reference. CAP: community-acquired pneumonia, CI: confidence interval, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, HCAP: healthcare-associated pneumonia, NTM: nontuberculous mycobacteriosis, OR: odds ratio

rhabdomyolysis showed hypophosphatemia, and rhabdomyolysis was associated with hypophosphatemia in a univariable analysis. Hypophosphatemia can cause rhabdomyolysis (36) by mechanisms such as impaired mitochondrial respiration and oxidative phosphorylation in skeletal muscle (37, 38). The limited number of patients with rhabdomyolysis may be a reason that neither hypophosphatemia nor rhabdomyolysis showed a significant association with mortality in our multivariable analysis.

Several limitations associated with the present study warrant mention. First, because this was a retrospective, observational study, the level of confidence is reduced, and a complete diagnostic workup to determine etiology was not possible in every patient. Second, this was a single-center study, and the results may not be applicable in other settings. Finally, our study was limited to patients in whom serum phosphorus was measured, so there may have been some bias in the patient selection.

Conclusion

The significance for clinicians of hypophosphatemia in patients with pneumonia lies in the laboratory findings that predict abnormal glucose metabolism, *Legionella* infection, and severe disease. However, hypophosphatemia was not associated with the prognosis in our patients with pneumonia. Patient characteristics (PS, comorbidities), laboratory findings (bacteremia), disease severity on admission, and antimicrobial treatment after admission contributed to their prognosis.

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