

Relationship between serum vitamin D concentrations and clinical outcome of community-acquired pneumonia

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SUMMARY

SETTING: Hospitalised patients with community-acquired pneumonia (CAP) in a tertiary referral hospital in South Korea.

OBJECTIVE: To determine the burden of vitamin D deficiency in patients hospitalised with CAP and to investigate whether vitamin D deficiency affected clinical outcomes.

DESIGN: Serum 25-hydroxyvitamin D (25[OH]D) levels were measured at admission; vitamin D deficiency was defined as 25(OH)D <20 ng/ml. Data were retrospectively analysed for incidence of vitamin D deficiency. The primary outcome was the relationship between serum vitamin D concentration and 28-day all-cause mortality in CAP.

RESULTS: The mean age was 68.1 years (standard deviation [SD] ± 14.6), and the mean pneumonia

severity index was 98.0 (±SD 28.6). Of the 797 patients (males 66.0%), 641 (80.4%) had vitamin D deficiency. Overall mean serum 25(OH)D level was 14.0 ± 7.4 ng/ml. The 28-day all-cause mortality rate in vitamin D-deficient patients was significantly higher than in non-deficient patients (8.3% vs. 2.6%, $P=0.01$), and serum vitamin D level was negatively associated with risk of 28-day mortality in CAP after adjustment for pneumonia severity index and serum lactate levels (OR 0.94, 95%CI 0.90–0.99, $P < 0.01$).

CONCLUSION: The prevalence of vitamin D deficiency was ~80% in patients hospitalised with CAP. Vitamin D deficiency was also a significant predictor of increased 28-day all-cause mortality.

KEY WORDS: calcifediol; 25(OH)D; vitamin D deficiency; pneumonia severity index

CLASSICALLY BELIEVED TO BE primarily responsible for calcium and bone homeostasis, reduced serum vitamin D levels have also been reported to be associated with respiratory infection, heart failure, mortality in critically ill patients and even some malignancies.^{1–5} However, apart from the regulation of calcium and bone metabolism, there is no consensus on the serum vitamin D level(s) that are appropriate for its various roles. Vitamin D deficiency is generally defined as 25-hydroxyvitamin D (25[OH]D) <20 ng/ml.⁶

Vitamin D deficiency is common worldwide in winter due to decreased outdoor activity and thus sun exposure, especially in the elderly.^{7,8} Pneumonia is also a common disease associated with considerable morbidity and mortality, despite preventive vaccination and effective antibiotic treatment.⁹

The biologically active form of vitamin D, 1,25-dihydroxyvitamin D, has been shown to be a potent modulator of the adaptive immune system and to

stimulate innate immune responses upon infection.¹⁰ Several studies have shown an association between vitamin D deficiency and increased susceptibility to respiratory tract infections.^{8,11–13} In the present study, we sought to investigate whether vitamin D status was associated with clinical outcomes in patients hospitalised with community-acquired pneumonia (CAP).

METHODS

Patients and study design

This was a retrospective observational study. We reviewed the medical records of patients aged ≥18 years who were admitted for CAP between March 2012 and February 2014.

Pneumonia was diagnosed based on respiratory symptoms such as cough, sputum and dyspnoea, and/or systemic symptoms such as fever, chills and weakness, plus radiographic abnormalities such as

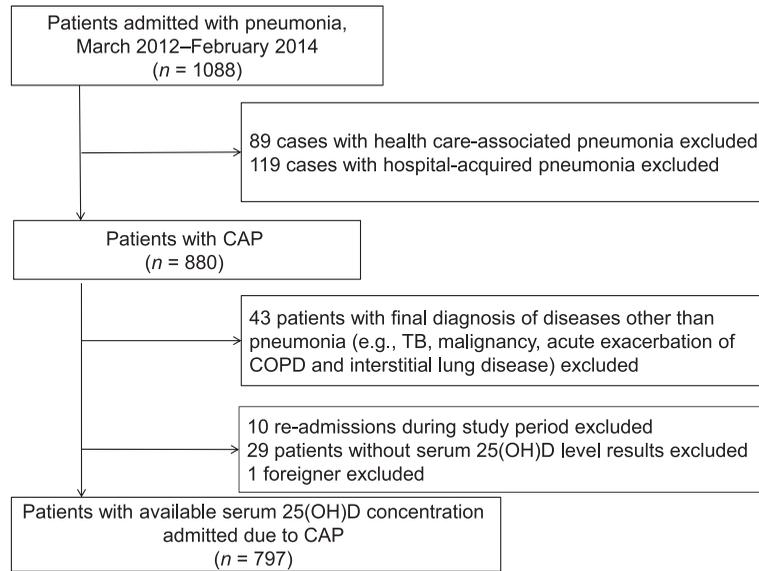


Figure 1 Flow diagram of study participants. CAP = community-acquired pneumonia; 25(OH)D = 25-hydroxyvitamin D; TB = tuberculosis; COPD = chronic obstructive pulmonary disease.

newly developed lesions on chest radiograph or computed tomography scan. Patients with non-infectious diseases, such as hypersensitivity pneumonitis, eosinophilic lung disease, obstructive pneumonitis and any related malignancy, were excluded. Furthermore, cases of pulmonary tuberculosis or lung malignancy diagnosed after discharge were excluded from the analysis. Patients with active ongoing chemotherapy or an immunocompromised status were not enrolled (Figure 1).

Patient data included baseline demographic characteristics, Charlson comorbidity index (CCI),¹⁴ pneumonia severity index (PSI), CURB-65 (confusion, uraemia, respiratory rate, low blood pressure, age ≥ 65 years) and clinical laboratory data. All patients included in this study were treated with antibiotics according to the Korean treatment guidelines for community-acquired pneumonia.¹⁵

Serum vitamin D concentrations

Blood samples were collected at admission, and serum concentrations of 25(OH)D were determined using a chemiluminescent immunoassay at the Green Cross Laboratory, Daegu, South Korea. Vitamin D deficiency was defined as 25(OH)D < 20 ng/ml (50 nmol/l).⁶

Outcome measure

The primary endpoint was death within 28 days of hospital admission (28-day all-cause mortality). Other clinical outcome variables included need for mechanical ventilation, duration of intensive care unit (ICU) stay, duration of hospitalisation and prevalence of vitamin D deficiency in in-patients with CAP.

Statistical analyses

Descriptive statistics included frequencies and percentages for categorical variables and means and standard deviations (SDs). All CAP in-patients finally enrolled in this study were classified into vitamin D-deficient and non-deficient groups. To compare continuous variables, the *t*-test or the Mann-Whitney *U*-test was used, as appropriate. To analyse categorical variables, a χ^2 analysis or Fisher's exact test was used. The odds ratios (ORs) for 28-day all-cause mortality were estimated, adjusting for potential confounders such as PSI (including age, sex and chronic illness) and serum lactate level. To examine the relationship between vitamin D deficiency and 28-day mortality in CAP, we fitted a logistic regression model with the categorical variable (vitamin D deficiency vs. non-deficiency) and the continuous variable of serum 25(OH)D concentration. To evaluate the performance of the model, receiver operating characteristic (ROC) curve analysis with area under an ROC curve (AUC) statistics were assessed.

Data were analysed using SPSS software, version 17.0 for Windows (Statistical Package for the Social Sciences, Chicago, IL, USA). All tests were 2-tailed, and $P \leq 0.05$ was considered to indicate statistical significance.

Ethics statement

The present study was approved by the Institutional Review Board of the Yeungnam University Hospital, Daegu, South Korea; patient data and information were confidential.

Table 1 Baseline characteristics of enrolled patients

Characteristic	Serum 25(OH)D level		P value
	<20 ng/ml n (%)	≥20 ng/ml n (%)	
Total	641 (100)	156 (100)	
Female	230 (35.9)	41 (26.3)	0.02*
Age, years, mean ± SD	67.8 ± 14.7	69.3 ± 14.4	0.27
Smoking, pack-years, mean ± SD	13.3 ± 23.4	12.9 ± 21.7	0.86
Pneumonia severity index, mean ± SD	98.3 ± 29.1	96.5 ± 26.6	0.49
CURB-65, mean ± SD	1.5 ± 1.0	1.4 ± 0.9	0.25
Charlson comorbidity index, mean ± SD	1.5 ± 1.5	1.2 ± 1.2	0.02*
Comorbidities			
Cardiovascular disease	103 (16.1)	25 (16.0)	0.99
Chronic pulmonary disease	214 (33.4)	47 (30.1)	0.44
Cerebrovascular disease	106 (16.5)	28 (17.9)	0.67
Diabetes mellitus	139 (21.7)	28 (17.9)	0.30
Liver disease	22 (3.4)	2 (1.3)	0.16
Renal disease	29 (4.5)	3 (1.9)	0.14
Malignancy	82 (12.8)	13 (8.3)	0.12
Gastric ulcer	6 (0.9)	0 (0.0)	0.23
Connective tissue disease	16 (2.5)	1 (0.6)	0.15
MAP, mmHg, mean ± SD	88.4 ± 16.3	88.3 ± 16.6	0.26
Presence of shock (MAP <60 mmHg)	39 (6.1)	5 (3.2)	0.16
Lactic acid level, mmol/l, mean ± SD	1.8 ± 1.3	1.5 ± 0.9	<0.01*
Initial PaO ₂ /FiO ₂ , mean ± SD	237.6 ± 159.0	258.7 ± 158.8	0.14
Serum 25(OH)D, ng/ml, mean ± SD	11.1 ± 4.2	26.1 ± 5.3	<0.01

* $P < 0.05$.

25(OH)D = 25-hydroxyvitamin D; SD = standard deviation; CURB-65 = confusion, uraemia, respiratory rate, low blood pressure, age ≥65 years; MAP = mean arterial pressure; PaO₂ = partial oxygen pressure; FiO₂ = fraction of inspired oxygen.

RESULTS

Baseline characteristics

The total number of patients admitted to our hospital with pneumonia during the study period was 1088. After the exclusion of patients with health care-associated and hospital-acquired pneumonia, 880 patients with CAP remained. After excluding malignancies, duplication, non-infectious pneumonitis and tuberculosis, 826 patients were enrolled. Of these, 29 patients without serum 25(OH)D level results on admission were excluded. Data on a final 797 patients were analysed (Figure 1).

The mean age of the enrolled patients was 68.1 years (± standard deviation [SD] 14.6, range 18–96); 526 (66.0%) were males. The numbers of patients belonging to Groups III (PSI 71–90), IV (PSI 91–130) and V (PSI ≥131) were respectively 180 (22.6%), 396 (49.7%) and 98 (12.3%). The baseline characteristics of the enrolled patients are shown in Table 1.

Prevalence of 25(OH)D deficiency

The mean serum 25(OH)D concentration of CAP patients in this study was 14.1 ± SD 7.6 ng/ml. Of the 797 total study patients, 641 (80.4%) were vitamin D-deficient (<20 ng/ml), with an average concentration of 11.1 ± SD 4.2 ng/ml. Only 27 (3.4%) patients satisfied the serum vitamin D concentration level

recommended by the American Clinical Endocrinology Society, of >30 ng/ml.⁶

The proportion of females was higher in the vitamin D-deficient than in the non-deficient group (35.9% vs. 26.3%, $P = 0.02$). PSI and CURB-65 were not significantly different between the vitamin D-deficient and non-deficient groups. However, CCI and serum lactate levels were higher in vitamin D-deficient than in non-deficient patients.

Seasonal variation in serum 25(OH)D levels

Seasonal variation in serum 25(OH)D concentrations was observed in the study population (Figure 2). The year was divided into four seasons of 3-month intervals, starting with March (spring). The mean serum 25(OH)D concentrations were highest in autumn and lowest in winter. The proportion of vitamin D-deficient patients was highest in winter.

Relationship between serum 25(OH)D level and clinical outcomes

The overall 28-day mortality in the study population was 7.7% (57/797). Twenty-eight-day mortality, the primary outcome, was significantly higher in the vitamin D-deficient than in the non-deficient group (8.3% vs. 2.6%, $P = 0.01$). In univariate analysis, the OR of 28-day all-cause mortality in vitamin D-deficient patients was 3.43 (95% confi-

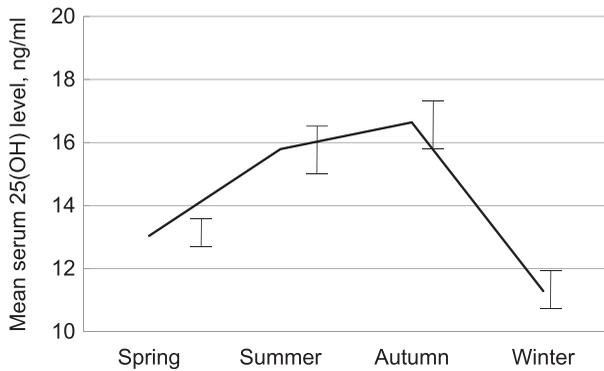


Figure 2 Seasonal variation in the mean serum 25(OH)D levels. The mean serum 25(OH)D concentration was highest, at 16.9 ng/ml, in autumn and lowest, at 11.3 ng/ml, in winter. Error bar represents ± 1 standard error. 25(OH)D = 25-hydroxyvitamin D.

dence interval [CI] 1.22–9.61, $P = 0.02$) vs. non-deficient patients. This result was significant after adjustment for PSI, when the adjusted OR of 28-day mortality in the vitamin D-deficient group was 3.31 (95%CI 1.17–9.39, $P = 0.03$). The need for mechanical ventilation, duration of ICU and length of hospitalisation did not differ significantly between the groups (Table 2).

In addition, 28-day all-cause mortality was correlated inversely with serum 25(OH)D levels. This association was also significant after adjusting for PSI and serum lactate levels (Table 3). As shown in Figure 3, AUC statistics for 28-day all-cause mortality based on PSI and combination of PSI and serum vitamin D level were respectively 0.72 (95%CI 0.66–0.78) and 0.74 (95%CI 0.67–0.80). Based on the combination of PSI, serum vitamin D and lactate levels, the AUC for 28-day mortality was 0.80 (95%CI 0.74–0.85).

DISCUSSION

In this study, 80% of in-hospital patients with CAP had vitamin D deficiency on admission. In particular, vitamin D deficiency was more common in females than males, those who had more comorbid conditions and during winter. Moreover, vitamin D deficiency was significantly related to increased 28-day all-cause mortality of CAP. The 28-day all-cause mortality was correlated inversely to serum 25(OH)D levels after adjustment for PSI and serum lactate level.

In total, 123 (15.4%) patients with PSI < 70 were included in this study. They required hospitalisation due to pleural effusion, inability to take oral medicines, severe hypoxaemia or decompensated coexisting illness. However, given their young age, their PSI level did not require hospital admission. As patients with less severe illness were included and as this investigation was conducted at a tertiary referral hospital, the overall study mortality (mean PSI $98 \pm$

Table 2 Clinical outcomes by serum 25(OH)D level

Clinical outcome	Serum 25(OH)D level		P value
	< 20 ng/ml n (%)	≥ 20 ng/ml n (%)	
28-day all-cause mortality	53 (8.3)	4 (2.6)	0.01*
Need for mechanical ventilator	38 (5.9)	5 (3.2)	0.18
Duration of ICU stay, days, mean \pm SD	19.9 \pm 28.9	11.5 \pm 9.0	0.57
Duration of hospitalisation, days, mean \pm SD	12.5 \pm 15.4	10.3 \pm 11.0	0.57

* $P < 0.05$.

25(OH)D = 25-hydroxyvitamin D; ICU = intensive care unit; SD = standard deviation.

SD 28.6) of 7.2% was reasonable compared with the 9.3% 30-day mortality predicted for Group IV (PSI 91–130) in the Port validation study.¹⁶

While PSI and CURB-65 values did not differ between the 25(OH)D-deficient and non-deficient groups, the CCI was higher in the 25(OH)D-deficient than in the non-deficient group. Given the observational nature and cross-sectional design of our investigation, it is uncertain whether vitamin D deficiency is a cause of the higher CCI or a result of more comorbid conditions that limited outdoor activity.

According to recent studies on vitamin D and respiratory disease, vitamin D insufficiency may be a contributing factor in increased susceptibility to respiratory tract infection,^{8,11,12,17} and serum 25(OH)D levels had a negative correlation with pneumonia severity and hospitalisation.^{17–19} However, the severity of pneumonia as assessed by PSI and CURB-65 was not associated with serum 25(OH)D concentration in this study. Because factors other than serum 25(OH)D level, such as virulence of the causative organism, individual nutritional status and vaccination, could affect disease severity, this result was not conclusive.

Some investigators have hypothesised that vitamin D influences immune system function through the antimicrobial peptides cathelicidin and beta-defensin-2, but no significant correlation was found between serum 25(OH)D and cathelicidin or beta-defensin-2 levels.² Although the mechanisms of the immunological functions of vitamin D are not yet clear, dysfunctional macrophage activity was evident at lower serum 25(OH)D concentrations.²⁰

In line with the results of this study, several investigations have reported an association between vitamin D deficiency and adverse outcomes in CAP.^{2,21} However, in this study the prevalence of vitamin D deficiency was much higher (80% vs. 53%), and vitamin D deficiency was more common in women. Serum vitamin D levels were affected by various factors such as latitude, seasons, diet and race. It is therefore relevant to investigate the

Table 3 ORs of 28-day all-cause mortality of CAP by serum 25(OH)D concentration

	28-day all-cause mortality of CAP		
	Unadjusted OR (95%CI)	Model 1* OR (95%CI)	Model 2† OR (95%CI)
Serum 25(OH)D, ng/ml	0.93 (0.89–0.98)	0.94 (0.90–0.99)	0.94 (0.90–0.99)
PSI		1.03 (1.02–1.04)	1.02 (1.01–1.03)
Lactate, mmol/l			1.41 (1.20–1.65)

* Adjusted for PSI.

† Adjusted for PSI and serum lactic acid levels.

OR=odds ratio; CAP=community-acquired pneumonia; CI=confidence interval; 25(OH)D=25-hydroxyvitamin D; PSI=pneumonia severity index.

prevalence of vitamin D deficiency in other cohorts and assess the relationship between vitamin D deficiency and several diseases, such as pneumonia, critical illness, heart failure and malignancy. Although retrospective in design, the study included about 800 patients admitted for new-onset CAP (health care-associated and hospital-acquired pneumonia were excluded).

The present study had a retrospective observational design, which has known limitations. First, the question of whether a vitamin D supplement could improve mortality should be evaluated by means of a randomised controlled trial. Moreover, the definition of vitamin D 'deficiency' was based on a bone and mineral metabolism standard, and it is still unknown what level is appropriate for the

immunological role of 25(OH)D. It was reported that 25(OH)D levels <30 ng/ml were associated with a significant increase in the risk of CAP.¹² However, target vitamin D levels and the optimal dose of vitamin D for immunological functions remain uncertain. A randomised trial of bolus-dose vitamin D supplementation to infants failed to reduce the incidence of first episodes of pneumonia in Kabul, Afghanistan.²² There is a need to modify the route, dose and interval of vitamin D supplementation and to reset target levels.²³

As this study was carried out at a single centre, careful interpretation is required. The common causative pathogen(s) of pneumonia, the antibiogram of the bacteria and average serum vitamin D concentrations could vary according to geographic location and could influence the clinical outcome of CAP.

Vitamin D supplementation has only minor side effects, such as increased risk of urinary calcium stones, and costs are not high in most countries. Although further research is necessary to determine whether supplementation with vitamin D is beneficial, in the light of its potential benefits, vitamin D supplementation could be a useful strategy for both preventing and treating respiratory infection.^{11,18,24}

In conclusion, vitamin D deficiency was highly prevalent in patients admitted to a tertiary hospital with CAP in Korea. In addition to its high prevalence, vitamin D deficiency was significantly related to higher 28-day all-cause mortality in CAP. Physicians should be aware of vitamin D deficiency and consider its management, particularly in females and in patients with a number of chronic illnesses.

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Conflicts of interest: none declared.

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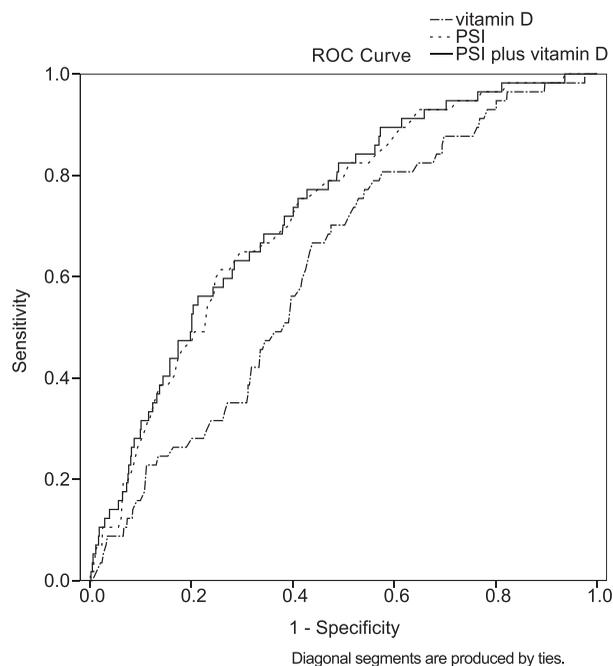


Figure 3 ROC curve analysis of the prediction of 28-day mortality based on serum vitamin D level, PSI, and combination of serum vitamin D level and PSI. AUC statistics for 28-day mortality based on vitamin D, PSI and combination of both were 0.62 (95%CI 0.55–0.69), 0.72 (95%CI 0.65–0.78) and 0.74 (95%CI 0.65–0.78), respectively. ROC = receiver operating characteristics; PSI = pneumonia severity index; AUC = area under the ROC curve.

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RESUME

CONTEXTE : Des patients hospitalisés pour une pneumonie acquise en communauté (CAP) dans un hôpital de référence tertiaire en Corée du Sud.

OBJECTIF : Déterminer l'ampleur du déficit en vitamine D chez des patients hospitalisés avec une CAP et étudier s'il a été associé à l'évolution clinique.

SCHEMA : Le taux sérique de 25-hydroxy vitamine D (25[OH]D) a été mesuré lors de l'admission et le déficit en vitamine D a été défini comme le 25(OH)D <20 ng/ml. Les données ont été analysées rétrospectivement en termes d'incidence du déficit en vitamine D. Le résultat principal a été la relation entre la concentration sérique en vitamine D et la mortalité toutes causes confondues en 28 jours lors d'une CAP.

RESULTATS : L'âge moyen (\pm déviation standard) était de 68,1 \pm 14,6 ans et l'index de gravité moyen de la

pneumonie a été de 98,0 \pm 28,6. Parmi les 797 patients (dont 66,0% d'hommes), 641 (80,4%) avaient un déficit en vitamine D. Le taux sérique d'ensemble du 25(OH)D a été de 14,0 \pm 7,4 ng/ml. Le taux de mortalité de toutes causes pendant 28 jours s'est avéré significativement plus élevé chez les patients déficients en vitamine D que chez les patients non déficients (8,3% contre 2,6% ; $P = 0,01$) et le taux sérique de vitamine D a été négativement associé au risque de mortalité en 28 jours en cas de CAP après ajustement sur le PSI et le taux sérique de lactates (OR 0,94 ; IC95% 0,90–0,99 ; $P < 0,01$).

CONCLUSION : La prévalence du déficit en vitamine D a été d'environ 80% chez des patients hospitalisés pour CAP. Le déficit en vitamine D a également été un facteur prédictif significatif d'élévation de la mortalité de toutes causes en 28 jours.

RESUMEN

MARCO DE REFERENCIA: Los pacientes hospitalizados por neumonía extrahospitalaria en un establecimiento de atención terciaria de referencia en Corea del Sur.

OBJETIVO: Determinar la carga de morbilidad por deficiencia de vitamina D en los pacientes hospitalizados por neumonía adquirida en la comunidad e investigar si esta deficiencia se asocia con los desenlaces clínicos.

MÉTODO: Se determinó la concentración sérica de 25 hidroxivitamina D (25[OH]D) en el momento de la hospitalización y se definió la deficiencia como una concentración inferior a 20 ng/ml. Se analizaron de manera retrospectiva los datos sobre la incidencia de deficiencia de vitamina D. El primer criterio de valoración fue la correlación entre la concentración sérica de vitamina D y la mortalidad por todas las causas a los 28 días, en los casos de neumonía extrahospitalaria.

RESULTADOS: La media de la edad de los pacientes fue 68,1 años (desviación estándar [SD] \pm 14,6 años) y el promedio del índice de gravedad de la neumonía fue

98,0 (\pm SD 28,6). De los 797 pacientes (66,0% de sexo masculino), 641 presentaron deficiencia de vitamina D (80,4%). La media global de la concentración sérica de 25(OH)D fue 14,0 ng/ml (\pm SD 7,4 ng/ml). La tasa de mortalidad por todas las causas a los 28 días en los pacientes con deficiencia de vitamina D fue significativamente más alta que en los pacientes sin deficiencia (8,3% contra 2,6%; $P = 0,01$) y la concentración sérica presentó una correlación negativa con el riesgo de mortalidad a los 28 días en este grupo de pacientes, tras corregir con respecto al índice de gravedad de la neumonía y la concentración sérica de lactato (OR 0,94; IC95% 0,90–0,99; $P < 0,01$).

CONCLUSIÓN: La prevalencia de deficiencia de vitamina D fue cercana a 80% en los pacientes hospitalizados por neumonía extrahospitalaria. Esta deficiencia vitamínica fue además un factor pronóstico significativo de una mayor mortalidad por todas las causas a los 28 días.