MAJOR ARTICLE

Addition of Vitamin D Status to Prognostic Scores Improves the Prediction of Outcome in Community-Acquired Pneumonia

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Background. Vitamin D plays a role in host defense against infection. Vitamin D deficiency is common worldwide. The prognostic value of vitamin D levels in pneumonia is unknown.

In this study, we aimed to investigate the impact of vitamin D status on outcome in community-acquired pneumonia (CAP).

Methods. We conducted a prospective cohort study in 272 hospitalized patients with CAP. Levels of 25-hydroxyvitamin D, leukocytes, C-reactive protein, and total cortisol and the Pneumonia Severity Index (PSI) and CURB-65 scores were measured on admission. Major outcome measures were intensive care unit (ICU) admission and 30-day mortality.

Results. One hundred forty-three patients (53%) were vitamin D deficient (<50 nmol/L), 79 patients (29%) were vitamin D insufficient (50–75 nmol/L), and 50 patients (18%) were vitamin D sufficient (>75 nmol/L). Vitamin D deficiency was associated with an increased risk of ICU admission and 30-day mortality. Vitamin D status was an independent predictor of 30-day mortality (area under the curve [AUC] = 0.69; 95% confidence interval [CI], .57–.80). Multivariate regression analysis including all predictors for outcome resulted in a final model including vitamin D status and the PSI score, with a significantly higher prognostic accuracy compared with the PSI score alone (AUC = 0.83; 95% CI, .71–.94).

Conclusions. Vitamin D deficiency is associated with adverse outcome in CAP.

Vitamin D status is an independent predictor of 30-day mortality and adds prognostic value to other biomarkers and prognostic scores, in particular the PSI score.

Clinical Trials Registration. NCT00471640.

Community-acquired pneumonia (CAP) is a common disease with considerable morbidity and mortality, despite preventive vaccinations and effective antibiotic treatment. Together with influenza, CAP is the eighth leading cause of death in persons aged >65 years in the United States, and is the leading infectious cause of death worldwide [1]. New targets are needed in the assessment and management of CAP, to better guide the therapeutic options and ultimately improve clinical outcome.

Recently, there has been much interest in the role of vitamin D in host defense against infection. Apart from its classical function in calcium-phosphate

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homeostasis, vitamin D has pleiotropic immunomodulatory properties. Vitamin D plays an important role in the innate immune response, in particular by increasing the production of antimicrobial peptides (β-defensin, cathelicidin) [2]. Furthermore, vitamin D has profound effects on the activity of the adaptive immune system through its interaction with the vitamin D receptor expressed by dendritic cells, monocytes, T cells, and B cells [2].

Vitamin D deficiency is very common worldwide, particularly in risk groups such as the elderly and people living distant from the equator [3, 4]. The main sources of vitamin D in humans are synthesis in the skin following exposure to ultraviolet B radiation in sunlight, diet, and dietary supplements. Accordingly, vitamin D deficiency can result from inadequate sun exposure, insufficient nutrition, or malabsorption.

Several studies have shown an association between vitamin D deficiency and increased susceptibility to respiratory tract infections [5–9]. Up to now, only one study has investigated the relationship between 25-hydroxyvitamin D levels and clinical outcome in adult patients with CAP [10]. Vitamin D deficiency (serum 25-hydroxyvitamin D <50 nmol/L) was present in 44% of the patients, of which 15% were severely deficient (serum 25-hydroxyvitamin D <30 nmol/L). In this study, vitamin D deficiency was associated with increased 30-day mortality in patients admitted to the hospital with CAP during wintertime. However, this study lacked information about the prognostic value of vitamin D status.

Because the prognostic value of vitamin D status in CAP is currently unknown, we undertook this study to determine the impact of vitamin D status on clinical outcome in a well-defined cohort of CAP patients in the Netherlands, a Western European country which is located on the latitude of 52°N. We investigated the contribution of vitamin D status to the prognostic accuracy of other biomarkers and commonly used prognostic scores. Our hypothesis is that a low 25-hydroxyvitamin D level is related to adverse outcome, due to the lack of immunomodulatory activities in case of deficiency.

METHODS

Patients and Study Design

This is a prospective cohort study that uses data from adult patients who participated in a randomized clinical trial that examined the effectiveness of dexamethasone in CAP. The details of the study population have been described previously and are summarized in the Supplementary Data [11]. The Pneumonia Severity Index (PSI) score and CURB-65 score were calculated on admission [12, 13]. Drug use before hospital admission (prescribed by the general practitioner) was registered. Patients receiving calcitriol or 1-α-hydroxyvitamin D3 were excluded, because these are likely to influence vitamin D status but are not measured by the 25-hydroxyvitamin D assay used. Patients receiving other formulations of vitamin D supplementation were included. The study was approved by the local Medical Ethics Committee, and all patients gave written informed consent.

Outcome Measures

The primary endpoint was adverse clinical outcome, defined as the need for intensive care unit (ICU) admission during hospitalization or death within 30 days of hospital admission (30-day mortality). Patients who were admitted to the ICU were in need of mechanical ventilation, vasopressor support, or both.

Serum Vitamin D Measurement

Blood serum samples were collected on admission and stored at −80°C. Serum 25-hydroxyvitamin D level was measured with the commercially available 25(OH)D TOTAL Liaison chemiluminescence assay (Liaison, Diasorin SpA, Saluggia, Italy). Based on this level, patients were categorized as deficient (<50 nmol/L), insufficient (50–75 nmol/L), and sufficient (>75 nmol/L) [14].

Measurement of Other Biomarkers

Leukocytes, C-reactive protein (CRP), and total cortisol were measured in serum on the day of presentation. Concentrations of CRP were measured with high-sensitivity CRP (Roche Diagnostics GmbH, Mannheim, Germany). The total serum cortisol level was measured with a solid-phase competitive enzyme-linked immunosorbent assay (Calbiotech, Spring Valley, California).

Statistical Analysis

Baseline characteristics were compared among the categories of vitamin D status using χ^2 test, Fisher exact test, 1-way analysis of variance, or Kruskal-Wallis test, where appropriate.

The association between vitamin D status and ICU admission or 30-day mortality was evaluated by univariate analysis, wherein vitamin D status was analyzed as a categorical variable.

To explore causality of the association, regression analysis was conducted focused on identifying confounding factors. To enlarge the number of confounders that could be tested, the combined endpoint mortality/ICU admission was used. We considered factors (from univariate analysis or previously mentioned in literature) as potential confounders when they were associated with both vitamin D deficiency and adverse outcome. We selected confounders for the multivariate model stepwise by direct estimation of the degree of confounding produced by each factor (relative change in the regression coefficient for adverse outcome associated with vitamin D deficiency). Factors that modified the regression coefficient by

≥10% were considered confounders. A final multivariate model was obtained including all identified confounding variables.

To examine the predictive value of vitamin D relative to other predictors for mortality from CAP, univariate and multivariate regression analysis was performed. All predictors significantly associated ($P < .05$) with mortality in the univariate analysis were entered simultaneously into a multiple backward logistic regression model. Predictors were sequentially deleted from the initial model on the basis of lack of significance ($P < .05$). To assess the discriminative qualities of the final model, receiver operating characteristic (ROC) curve analysis was performed. The goodness of fit of the final model was tested with the Hosmer-Lemeshow test.

All statistical analyses were performed using SPSS software version 18.0 (IBM SPSS, Chicago, Illinois). A 2-tailed *P* value <.05 was considered statistically significant.

RESULTS

A total of 304 patients were included in this study. After the exclusion of 7 patients who were using 1-α hydroxyvitamin D3 and 25 patients missing a 25-hydroxyvitamin D value, 272 patients remained for analysis. Mean age was 63.5 years (SD, 18.3), and 56% were male. In total, 15 patients (5.5%) were admitted to the ICU during their hospital stay, of whom 4 patients died. At day 30, 256 patients (94%) had survived, and 16 patients (5.9%) had died. Table 1 depicts the baseline characteristics of the study population, including stratification for vitamin D status.

Prevalence of Vitamin D Deficiency

In this cohort of Dutch patients with CAP, the median 25-hydroxyvitamin D level was 47.4 nmol/L (interquartile

Table 1. Baseline Characteristics of 272 Patients With Community-Acquired Pneumonia, Including Stratification for Vitamin D Status

Characteristic	All Patients (n = 272)	Vitamin D <50 nmol/L (n = 143)	Vitamin D 50–75 nmol/L (n = 79)	Vitamin D >75 nmol/L (n = 50)	*P* Value[a]
Sex, male	153 (56)	80 (56)	42 (53)	31 (62)	.61
Age, years, mean (SD)	63.5 (18.3)	66.7 (18.6)	61.1 (17.7)	58.3 (16.8)	<.01[c]
Race[b]					.69
White	270 (99)	141 (99)	79 (100)	50 (100)	
Other	2 (0.7)	2 (1)	0 (0)	0 (0)	
Nursing-home resident	13 (5)	11 (8)	2 (3)	0 (0)	.05[c]
Vitamin D supplementation	11 (4)	0 (0)	6 (8)	5 (10)	<.01[c]
Comorbidities					
Liver disease	2 (0.7)	2 (1)	0 (0)	0 (0)	.69
Renal disease	22 (8)	18 (13)	3 (4)	1 (2)	.02[c]
Heart failure	45 (17)	34 (24)	9 (11)	2 (4)	<.01[c]
Malignancy	17 (6)	11 (8)	3 (4)	3 (6)	.63
COPD	29 (11)	22 (15)	3 (4)	4 (8)	.02[c]
DM	39 (14)	28 (20)	8 (10)	3 (6)	.03[c]
Laboratory parameters					
Albumin (g/L)	42.0 (8.0)	41.1 (8.4)	42.7 (6.8)	43.5 (8.6)	.13
Leukocyte count ($\times 10^9$/L), mean (SD)	14.3 (6.5)	14.9 (7.0)	13.8 (6.5)	13.5 (4.8)	.32
CRP (mg/L), mean (SD)	212.9 (139.5)	203.9 (143.6)	232.3 (125.2)	207.9 (148.6)	.34
Cortisol (ng/mL), mean (SD)	221.9 (144.4–386.6)	255.2 (160.3–435.6)	196.4 (135.3–360.1)	186.0 (125.7–330.3)	.02[c]
CURB-65 score, median (IQR)	1.66 (1.2)	1.9 (1.2)	1.5 (1.2)	1.2 (1.1)	<.01[c]
PSI score	90.1 (36.4)	98.1 (36.7)	83.3 (32.7)	78.1 (36.1)	<.01[c]
PSI risk class					<.01[c]
I–III	147 (54)	63 (44)	49 (62)	35 (70)	
IV–V	125 (46)	80 (56)	30 (38)	15 (30)	

Data are presented as No. (%) unless otherwise specified.

Abbreviations: COPD, chronic obstructive lung disease; CRP, C-reactive protein; DM, diabetes mellitus; IQR, interquartile range; PSI, Pneumonia Severity Index; vitamin D, 25-hydroxyvitamin D; SD, standard deviation.

[a] Comparison of the three 25-hydroxyvitamin D categories.

[b] Self-reported.

[c] Characteristics showing a significant association with a *P* value <.05.

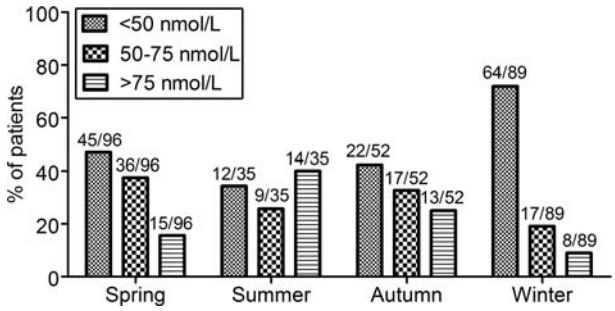

Figure 1. The prevalence of vitamin D deficiency throughout the astronomic seasons. The numbers above the bar indicate the number of patients within the related vitamin D category.

range [IQR], 30.4–68.2). Overall, 143 patients (53%) were vitamin D deficient (<50 nmol/L), 79 patients (29%) were vitamin D insufficient (50–75 nmol/L), and 50 patients (18%) were vitamin D sufficient (>75 nmol/L). Median 25-hydroxyvitamin D levels were lowest in patients presenting during the winter (21 December to 20 March; n = 89, 36.2 nmol/L [IQR, 25.9–51.4]), and highest in patients presenting in the summer (21 June to 20 September; n = 35, 70.6 nmol/L [IQR, 35.2–81.8]). The prevalence of vitamin D deficiency per season is shown in Figure 1. The 11 patients receiving vitamin D supplements (other than 1-α hydroxyvitamin D3) had significantly higher 25-hydroxyvitamin D levels than patients without vitamin D supplementation (74.6 nmol/L [IQR, 63.5–107.0] vs 45.3 nmol/L [IQR, 29.8–66.6]; $P < .01$).

Association Between Vitamin D Status and Clinical Outcome

Median 25-hydroxyvitamin D levels were significantly lower in patients who were admitted to the ICU, compared to patients without ICU admission (34.9 nmol/L [IQR, 23.8–46.3] vs 48.3 nmol/L [IQR, 30.8–68.4]; $P = .04$). Vitamin D deficiency was associated with a higher rate of ICU admission, compared with patients with vitamin D (in)sufficiency (Figure 2*A*).

Patients who died within 30 days had significantly lower 25-hydroxyvitamin D levels, compared with patients who survived (25.8 nmol/L [IQR, 19.8–40.1] vs 48.8 nmol/L [IQR, 32.4–68.9]; $P < .01$). Vitamin D deficiency was associated with a higher mortality rate, compared to patients with vitamin D (in)sufficiency (Figure 2*B*).

Identification of Confounding

In the crude analysis of the association between vitamin D status and clinical outcome, vitamin D deficiency was associated with an odds ratio (OR) of 4.60 (95% confidence interval [CI], 1.04–20.27) for the composite endpoint mortality/ICU admission. To explore possible causality of this association, we aimed to identify confounding factors. Race, sex, age, season of admittance, nursing-home residency, liver disease, renal disease, heart failure, malignancy, chronic obstructive pulmonary disease, diabetes mellitus, and serum albumin concentration on admission were all considered as potential confounders. Supplementary Table 1 lists the degree of statistical confounding by each factor in multivariate logistic regression analysis. Age and heart failure fulfilled our criteria of being confounders, and were retained in the final multivariate regression model. Table 2 lists the unadjusted and adjusted ORs for the association between vitamin D status and clinical outcome. An obvious trend toward a higher risk of adverse outcome among patients with vitamin D deficiency was observed after adjustment for confounders.

Vitamin D Status as Predictor for 30-Day Mortality From CAP

Based on the above-mentioned association between vitamin D deficiency and adverse outcome, vitamin D status on the day of admission could be a useful prognostic biomarker in patients with CAP. To assess the potential to predict 30-day mortality, we compared the predictive value of vitamin D

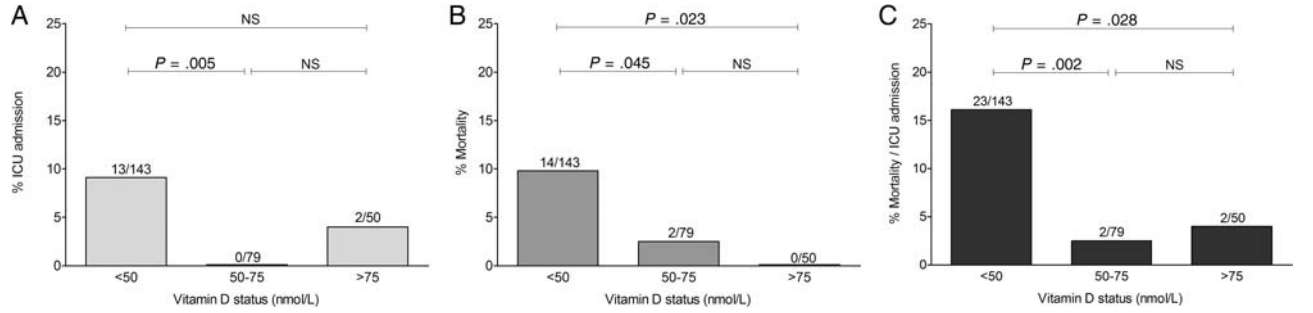

Figure 2. The rate of intensive care unit admission (*A*), 30-day mortality (*B*), and the composite endpoint mortality/ICU admission (*C*) stratified by serum 25-hydroxyvitamin D levels measured on presentation in patients with community-acquired pneumonia. Numbers above the bars indicate the number of patients with an adverse outcome. Abbreviations: ICU, intensive care unit; NS, not significant.

Table 2. Odds Ratios for the Association Between Vitamin D Status and Clinical Outcome Before and After Adjusting for Confounders

Vitamin D Status	No. of Patients (%) (n = 272)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]
25-hydroxyvitamin D >75 nmol/L	50 (18)	Reference	Reference
25-hydroxyvitamin D 50–75 nmol/L[a]	79 (29)	0.623 (.085–4.573)	0.510 (.068–3.807)
25-hydroxyvitamin D <50 nmol/L[a]	143 (53)	4.600 (1.044–20.272)	2.949 (.640–13.598)

Clinical outcome was the composite endpoint mortality/intensive care unit admission.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Compares patients with 25-hydroxyvitamin D levels between 50–75 nmol/L or <50 nmol/L with patients with 25-hydroxyvitamin D levels >75 nmol/L (reference category).

[b] Adjusted ORs for the confounders age and heart failure.

status with other commonly used predictors for prognosis in CAP by univariate and multivariate regression analysis. For statistical reasons (zero deaths within the category vitamin D sufficiency), and for practical application, we analyzed vitamin D–deficient patients (<50 nmol/L) vs other patients (≥50 nmol/L). We included the following predictors (all measured on the day of admission) in univariate regression analysis: vitamin D status (in 2 categories), leukocyte count (on a continuous scale), CRP level (on a continuous scale), cortisol level (on a continuous scale), PSI score (in 3 categories: 0–90 points, low risk; 91–130 points, intermediate risk; >130 points, high risk of 30-day mortality), and CURB-65 score (0–5 points, on a continuous scale). Four parameters appeared to be significant predictors for mortality, namely, vitamin D status, cortisol level, PSI score, and CURB-65 score. When vitamin D status was added to cortisol level, PSI score, and CURB-65 score individually, all prognostic accuracies improved (see Supplementary Table 2). Multivariate regression analysis including all 4 parameters resulted in a superior final model containing vitamin D status and PSI score. The Hosmer-Lemeshow goodness of fit test for the final model was not significant ($P = .94$), indicating that this model fits the data well. Figure 3 shows the ROC curves with the corresponding area under the curve (AUC) for the final model, together with the ROC curves and AUCs of vitamin D status and PSI score separately. With an AUC of 0.83 (95% CI, .71–.94), the prognostic accuracy of the combination of vitamin D status and PSI score was superior to the accuracy of the other predictors or the PSI score alone (AUC = 0.78 [95% CI, .64–.91]).

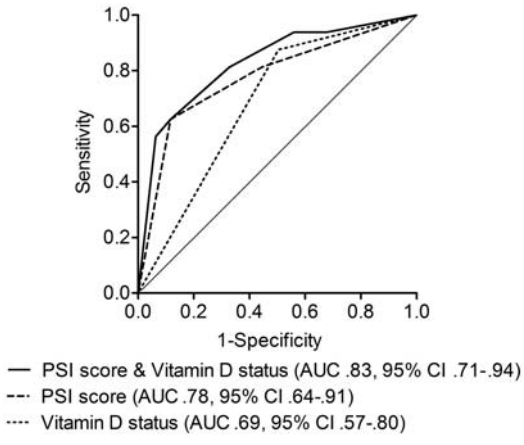

Figure 3. Receiver operating characteristic curve analysis of the prediction of 30-day mortality by Pneumonia Severity Index (PSI) score, vitamin D status, and the combined model "PSI score & vitamin D status." Data on the day of admission are shown. Abbreviations: AUC, area under the curve; CI, confidence interval; PSI, Pneumonia Severity Index.

DISCUSSION

Our study has 3 main findings. First, vitamin D deficiency is highly prevalent in this Dutch cohort of patients admitted to the hospital with CAP. Second, vitamin D deficiency is associated with adverse outcome. Third, vitamin D status on presentation is a significant predictor of 30-day mortality, and adds predictive value to other biomarkers and clinical scores. The combination of PSI score and vitamin D status appeared to be the best predictive model for 30-day mortality in CAP.

Vitamin D deficiency is very common in many populations worldwide, especially during the winter season [3, 15–19]. Vitamin D deficiency is not limited to particular risk groups, such as housebound and institutionalized elderly: high rates have also been reported in normal urban populations [18, 20]. The high prevalence of vitamin D deficiency found in our cohort of CAP patients is comparable to that reported in former studies in the general elderly population in the Netherlands [15, 21, 22].

To the best of our knowledge, only 2 studies in adults have investigated the association between vitamin D status and the course of infectious disease. Leow et al explored the relationship between vitamin D levels and clinical outcome in 112 adults admitted with CAP [10]. This study was carried out during the winter in Hamilton, New Zealand, which is

situated at a latitude of 37°S. They observed that vitamin D deficiency is associated with increased 30-day mortality. Ginde et al studied 81 adults who were evaluated for suspected infection at the emergency department [23]. They observed that vitamin D insufficiency is associated with higher sepsis severity. Our study confirms these previous findings (Figure 2).

In clinical practice, the PSI score and CURB-65 score are mostly used to predict 30-day mortality in patients with CAP. To date, several studies have investigated whether the inclusion of additional biomarkers would improve the 30-day mortality prediction of these 2 scores. Among others, the prognostic performance of CRP, procalcitonin, precursor peptides of endothelin-1, natriuretic peptides, proadrenomedullin, and cortisol have been evaluated, with variable, and sometimes promising, results [24–30]. The prognostic value of serum 25-hydroxyvitamin D has never been investigated. The comparison of the prognostic value of vitamin D status on presentation to the predictive ability of other biomarkers and clinical scores on CAP outcomes is a novel aspect of this work. Our study suggests that vitamin D status adds prognostic value to other biomarkers and prognostic scores. The combination of PSI score and vitamin D status appeared to be superior in prediction of 30-day mortality in CAP, with an AUC of 0.83 (Figure 3). C-reactive protein and cortisol were both inferior to vitamin D status in our study. A possible explanation for the predictive value of vitamin D status in CAP might be an indirect effect of poor physical or nutritional status. A direct effect could be the proven immunomodulatory activity of vitamin D. Although our predictive model is promising, further substantiation in future studies is needed. Before introduction in clinical practice can be considered, a large prospective study is needed to ultimately determine the best combination of biomarkers and clinical scores for prediction of outcome in CAP.

The finding of an association between vitamin D deficiency and adverse outcomes raises the question whether vitamin D supplementation in the acute care of CAP will improve outcome. The high prevalence of vitamin D deficiency in patients with CAP makes vitamin D a potential candidate for adjuvant treatment strategies. Recently, 2 randomized controlled trials assessed the effects of vitamin D supplementation in young children admitted with pneumonia. Choudhary et al demonstrated that short-term supplementation with oral vitamin D (1000–2000 IU per day for 5 days) had no beneficial effect on the duration of resolution of severe pneumonia in children <5 years. Unfortunately, no 25-hydroxyvitamin D levels were measured in this study. Hence, it cannot be ruled out that the recruited children were already vitamin D deficient and that the given doses were too low to cause an effect [31]. In the study of Manaseki-Holland et al, a single high dose of oral vitamin D3 (100 000 IU) upon admission did not result in a reduction of the duration of illness in children with pneumonia. However, they demonstrated a significant reduction in the occurrence of new episodes of pneumonia over a 90-day period [32]. The latter finding might also extend to adults, where an alternative option might be preventive vitamin D supplementation based on 25-hydroxyvitamin D measurement in high risk groups during wintertime, aimed at reaching a 25-hydroxyvitamin D level >75 nmol/L [33, 34]. Future research should further explore the capacity of vitamin D to play a preventive and/or therapeutic role in pneumonia.

Some limitations of our study should be mentioned. First, only a relatively small number of patients reached the study endpoint, which resulted in larger confidence intervals. This could have precluded reaching significance in some of the analyses, despite clear trends.

Second, to date, there is still no consensus on optimal 25-hydroxyvitamin D levels as measured in serum. In our analyses, patients were classified into the categories deficient (<50 nmol/L), insufficient (50–75 nmol/L), and sufficient (>75 nmol/L) [14]. However, in literature, different classifications of vitamin D status have been proposed. In order to rule out the possibility that other cutoffs would result in different predictive values, we conducted a sensitivity analysis by applying 2 other classifications (Supplementary Table 3) [4, 10]. In both cases, the rate of adverse outcome remained significantly higher for vitamin D–deficient patients. Interestingly, we observed that within the group of vitamin D–deficient patients, a 25-hydroxyvitamin D level <25 nmol/L or <30 nmol/L was associated with an even higher rate of adverse outcome (OR, 7.77 [95% CI, 1.62–37.30] and OR, 8.58 [95% CI, 2.70–27.31], respectively; Supplementary Table 3). Thus, the lower range of 25-hydroxyvitamin D seems to provide more contrast for a predictive model, and these cutoff values should therefore be further explored in future studies.

Finally, owing to the observational design of the study, we were not able to establish a causal relationship between vitamin D deficiency and adverse outcome. Although a trend toward higher risk persisted after adjustment for confounders, the presence of unmeasured confounding cannot be ruled out. Mainly, we lacked extensive information about nutritional status, body mass index and other lifestyle factors; nevertheless, we were able to include albumin as proxy for malnutrition.

In conclusion, vitamin D deficiency is highly prevalent in patients hospitalized with CAP in the Netherlands. We confirmed that vitamin D deficiency is associated with adverse outcome in CAP. Vitamin D status on presentation is a significant predictor for 30-day mortality, with additional prognostic value when combined with other biomarkers or prognostic scores, in particular the PSI score. Some clues for a possible causal relationship were found. Future studies should further

explore the likelihood of a causal relation between vitamin D deficiency and adverse outcome. In the case of a causal relationship, vitamin D supplementation might be a promising candidate for adjuvant treatment in CAP. Meanwhile, vitamin D status on presentation can be used as a prognostic marker.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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