Serum 25-hydroxyvitamin D levels in hospitalized adults with community-acquired pneumonia

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Abstract

Introduction: Community-acquired pneumonia (CAP) is the infectious disease with the highest number of deaths worldwide. Several studies have shown an association between vitamin D deficiency and increases susceptibility to respiratory tract infections.

Objective: The aim of this study was to evaluate the serum 25-hydroxyvitamin D (25OHD) levels in hospitalized adults in general room with CAP.

Materials and methods: An observational study was carried out in 207 hospitalized adults of both sex with CAP (>18 years) from Rosario city, Argentina (32° 52' 18" S) between July 2015 and June 2016.

Results: In total, 167 patients were included in the data analysis [59% women (57.4 ± 19.6 years), body mass index 27.2 ± 7.8 kg/m²]. In brief, 63% showed unilobar infiltrate and 37% were multilobar. The CURB-65 index was 66.5% low risk, 16.0% intermediate risk and 17.5% high risk. According to Charlson comorbidity index (CCI) 53.5% had not comorbidity (CCI 0) and 46.5% showed CCI ≥ 1. The 25OHD level was: 11.92 ± 7.6 ng/mL (51.5%: <10 ng/mL, 33.5%: 10–20 ng/mL, 13.2%: 20–30 ng/mL and 1.8%: >30 ng/mL). Higher 25OHD were found in male (female: 10.8 ± 6.7 ng/mL, male: 13.5 ± 8.5 ng/mL, P = .02) and 25OHD correlated with age (r = −.17; P = .02). 25-Hydroxyvitamin D was also correlated with CURB65 index (r = −.13; P = .049), CCI (r = −.20, P = .007) and with the 10 years of life expectative (%) (r = .19; P = .008). In addition, higher 25OHD were found with lower CCI (CCI 0 = 13.0 ± 8.2 ng/mL, CCI ≥ 1 = 10.5 ± 6.7 ng/mL; P = .0093).

Conclusions: Hospitalized adults with CAP have lower 25OHD levels and would be associated with the severity of CAP.

KEYWORDS
community-acquired pneumonia, comorbidity, severity, 25-hydroxyvitamin D
INTRODUCTION

Community-acquired pneumonia (CAP) is the infectious disease with the highest number of deaths worldwide. However, the importance of this disease is often underestimated. Community-acquired pneumonia incidence varied by country, age and gender, and is higher in individuals aged ≥65 years and in men. The annual incidence of CAP ranges from 2.7 to 10 per 1000 persons. Community-acquired pneumonia is diagnosed in an estimated 4.5 million patients annually in the United States, and 1.1 million requires hospitalization. Mortality varied from 1% to 48% and was associated with advanced age, co-morbid conditions and CAP severity. In outpatients, the mortality rate of pneumonia is low, close to 1%-5%, but in patients requiring hospitalization the mortality rate is ~12% and increases in those who develop bacteremia and require intensive care unit reaches almost 40%. In United States, CAP causes 15.9 deaths per 100 000 populations. In Argentina, it is the 6th cause of death in general and the 5th cause in people more than 60 years.

Several studies have shown that an association between vitamin D deficiency and increases susceptibility to respiratory tract infections. The importance of vitamin D on the regulation of immune cells has increased in the last decade with the discovery of the vitamin D receptor in these cells. Despite the demonstration of several immune-modulating effects of vitamin D/vitamin D receptor signaling, such as transcription of anti-microbial compounds and regulation of cytokine production and immune cell activity, the mechanisms underlying these relationships are still not fully understood.

The aim of this study was to evaluate the serum 25-hydroxyvitamin D (25OHD) levels in hospitalized adults with CAP and its relationship with CAP severity. In addition, the clinical characteristics of CAP were analyzed.

MATERIALS AND METHODS

Study design

An observational study in 207 hospitalized adults of both sex with CAP more than 18 years from Rosario city, Argentina (32°52′18″S), was carried out from July 2015 to June 2016 in 13 internal medicine service. The inclusion criteria were patients with CAP hospitalized in general room >18 years old who wanted to participate in this study and gave written informed consent. This study included patients fulfilling the following CAP criteria: (1) a new radiographic infiltrate and 2 or more of symptoms or signs (cough, sputum, dyspnea, fever, pleuritic chest pain, crackles or rhonchi); or (2) complicated parapneumonic effusion or empyema.

The exclusion criteria were as follows: CAP that was not the primary cause of hospitalization, patients hospitalized in the last 14 days, or who had previous history of neoplasia, acquired immune deficiency syndrome, chronic renal or liver disease, autoimmune or connective diseases, or were treated with glucocorticoids, anticonvulsants or vitamin D in the last year.

The study was approved by the Ethics Committee of School of Medicine, Rosario National University, Argentina, and was conducted in compliance with the Declaration of Helsinki.

Data collection

The baseline characteristics, biochemical determination and X-ray reports were obtained from medical records. The baseline characteristics recorded were sex, age, body mass index (BMI), smoking status, alcohol intake, medical history, previous medication (antibiotics, glucocorticoid, vitamin D supplementation, immunosupresors) and CAP symptoms. Blood pressure, cardiac and respiratory rate, body temperature, hemoculture and sputum culture were considered. The clinical course was measured by days of hospitalization, severe complications and in-hospital mortality. In addition, the CURB-65 index (Confusion, Urea, Respiratory rate, Blood pressure, age ≥65 years) was evaluated as a CAP severity parameter and the Charlson comorbidity index (CCI) and the 10 years of life expectative (%) were calculated with age and CCI were considered as comorbidity index.

Biochemical determination

General biochemical determinations were performed, including a full blood count, renal and liver function tests. The total 25OHD levels (D2 and D3) were determined by
chemiluminescence assay (ADVIA Centaur Vitamin D Total Assay—Siemens) in the first 48 hours of hospitalization and measured in a centralized laboratory. The 25OHD levels were classified as: severe deficiency as 25OHD levels <10 ng/mL, deficiency as 25OHD levels between 10 and 20 ng/mL, insufficiency as 25OHD levels between 20 and 30 ng/mL (50–75 nmol/L) and 25OHD levels of >30 ng/mL were considered as optimal. 17

### 2.4 Statistical analyses

Categorical variables were expressed as number (percentages) and continuous variables as mean ± standard deviation (SD) for normally distributed data or media (25th-75th percentiles) for sewed data as evaluated by the Kolmogorov–Smirnov test. Baseline characteristics were compared among the categories of serum 25OHD levels using $\chi^2$, Fisher exact test, one-way ANOVA or Kruskal–Wallis test, where appropriate. The differences were considered significant if $P < .05$. Statistical analyses were performed with GraphPad Prism 2.0 (GraphPad, San Diego, California).

## 3 RESULTS

A total of 207 patients with CAP were recruited, and 167 were finally included in this study. Forty patients were excluded because of incomplete data collection or a radiographic infiltrate or because of other cause. The included patients were 59% women and 41% men. The mean age was 57.4 ± 19.6 years (range, 18–96), the body mass index was 27.2 ± 7.8 kg/m².

The baseline characteristics and medical history of hospitalized adults with CAP in the whole group and according 25OHD levels is summarized in Table 1. A significant difference in age was observed between the groups with 25OHD <10 ng/mL and 25OHD 10–20 ng/mL, but no differences were found between the groups with 25OHD <10 ng/mL and 25OHD >20 ng/mL. In addition, higher proportion of women in the group with 25OHD <10 ng/mL was found. No differences were observed in symptoms and physical examination of hospitalized adults with CAP in the whole group corresponding 25OHD levels (Table 2).

Furthermore, no differences were observed in biochemical measurement of hospitalized adults with CAP in the whole group and corresponding 25OHD levels (Table 3).
No differences were observed in corresponding 25OHD levels (data not shown).

In the X-ray, 63% of the patients showed unilobar infiltrate and in 37% a multilobar infiltrate was observed. Unilateral pleural effusion was found in 11% and only 4% was bilateral. Only one patient had atelectasis and in another a unilobar cavitation was observed.

Blood cultures were performed in 95% of the patients and only 14% were positive (67% Streptococcus pneumoniae, 15% Klebsiella pneumoniae, 12% Serratia, 6% Staphylococcus aureus).

The sputum culture was requested in 58% of the cases and only 14% were positive (67% S. pneumoniae, 16% Streptococcus viridans, 16% Pseudomonas aeruginosa, 11% S. aureus, 10% Haemophilus influenzae, 5% K. pneumoniae and 5% enterobacter).

Pleural effusion culture was performed in 4.6% of the patients, being positive in 14.3%.

Ampicillin–sulbactam (39%) and ampicillin–sulbactam associated with clarithromycin (35%) were the most frequently used antibiotics.

The clinical follow-up showed sepsis (n = 7, 4.2%), sensory impairment (n = 7, 4.2%), acute renal failure (n = 5, 3%), respiratory failure (n = 4, 2.4%) and death (n = 3, 1.8%). No patient had deep venous thrombosis, pulmonary thromboembolism or extrapulmonary infection.

### 25-Hydroxyvitamin D levels in hospitalized adults with CAP

The 25OHD level in the whole group was 11.9 ± 7.6 ng/mL (51.5%: <10 ng/mL, 33.5%: 10–20 ng/mL, 13.2%: 20–30 ng/mL, 1.8%: >30 ng/mL). A significant correlation was found between 25OHD and age (r = −.17; P = .02). Furthermore, higher 25OHD were found in male (female: 10.8 ± 6.7 ng/mL, male: 13.5 ± 8.5 ng/mL, P = .02). Because of the characteristics of the pathology under study, 54% of the determinations were in winter, 28% spring, 2% summer and 15% autumn. As expected, 25OHD levels in winter–spring (11.0 ± 6.4 ng/mL) were lower than summer–autumn (16.1 ± 10.9 ng/mL, P = .01).

We did not find any correlation between 25OHD and C-reactive protein (CRP) or eritrosedimentation rate in our study (data not shown).

### 25-Hydroxyvitamin D levels according to severity and comorbidity scores

The CURB65 index was 66.5% low risk, 16.0% intermediate risk and 17.5% high risk. According to CCI, 53.5% had not comorbidity (CCI = 0) and 46.5% showed CCI ≥ 1.
TABLE 3  Biochemical measurement in hospitalized adults with CAP

|                        | All patients   | 25OHD <10 ng/mL | 25OHD 10–20 ng/mL | 25OHD >20 ng/mL | P value* |
|------------------------|---------------|-----------------|-------------------|----------------|---------|
|                        | (n = 167)     | (n = 86)        | (n = 56)          | (n = 25)       |         |
| Hematocrite (%)        | 37.8 (34.0–41.1) | 37.2 (33.8–41.4) | 38.0 (35.8–41.4) | 36.9 (33.5–40.5) | ns      |
| Hemoglobin (mg/dL)     | 12.5 (11.2–13.8) | 12.4 (10.9–13.8) | 12.9 (11.6–13.8) | 12.1 (11.1–14.1) | ns      |
| White blood cell count (10³/mm³) | 14.1 (9.6–18.4) | 14.1 (9.8–18.7) | 14.0 (9.7–18.3) | 14.5 (8.7–18.3) | ns      |
| Neutrophils (%)        | 83 (75–88)    | 84 (75–88)      | 81 (74–87)       | 83 (77–87)     | ns      |
| Lymphocytes (%)        | 10 (6–15)     | 10 (6–15)       | 10 (8–14)        | 12 (6–16)      | ns      |
| Platelets (mL/mm³)     | 241 (185–317) | 239 (173–318)   | 237 (184–311)    | 268 (202–337)  | ns      |
| Uremia (mg/dL)         | 36.5 (24.5–53.5) | 35.0 (26.0–55.0) | 42.0 (23.5–53.0) | 34.5 (24.0–66.5) | ns      |
| Creatinine (mg/dL)     | 0.9 (0.7–1.2) | 0.9 (0.7–1.2)   | 0.9 (0.6–1.2)    | 0.8 (0.7–1)    | ns      |
| Blood glucose (mg/dL)  | 118 (102–151) | 119 (102–158)   | 117 (101–151)    | 118 (103–139)  | ns      |
| Natremia (mEq/L)       | 135 (132–139) | 135 (132–140)   | 134 (132–137)    | 137 (132–140)  | ns      |
| Albuminemia (g/dL)     | 3.1 (2.5–3.4) | 3.1 (2.5–3.5)   | 2.8 (2.5–3.3)    | 3.1 (2.6–3.6)  | ns      |
| Total proteins (g/dL)  | 6.3 (6.0–6.9) | 6.4 (5.9–6.9)   | 6.3 (6.0–6.9)    | 6.3 (6.1–7.0)  | ns      |
| Aspartate transaminase (mUI/mL) | 23.0 (16.0–39.5) | 23.0 (17.5–39.5) | 23.0 (16.0–49.5) | 17.0 (12.5–38.5) | ns      |
| Alanine transaminase (mUI/mL) | 22.0 (17.0–38.5) | 22.0 (18.0–30.5) | 22.0 (15.0–55.0) | 23.0 (13.5–32.5) | ns      |
| Total alkaline phosphatase (UI/L) | 133 (84–205) | 139 (89–209) | 108 (74–190) | 158 (87–231) | ns      |
| Arterial pH             | 7.42 (7.39–7.45) | 7.42 (7.38–7.45) | 7.43 (7.40–7.45) | 7.43 (7.40–7.48) | ns      |
| PO₂                    | 72.0 (63.0–89.0) | 74.0 (62.0–89.0) | 70.5 (58.5–86.8) | 76.0 (64.5–87.5) | ns      |
| PCO₂                   | 32.6 (28.1–36.0) | 33.0 (28.0–37.0) | 32.3 (29.3–35.0) | 33.0 (28.0–34.0) | ns      |
| HCO₃                   | 21.0 (19.2–23.3) | 21.0 (18.3–23.3) | 21.0 (20.0–23.0) | 21.5 (19.9–24.5) | ns      |
| % Sat                  | 95.0 (92.0–96.7) | 94.4 (92.0–96.0) | 94.1 (90.0–97.0) | 95.5 (93.5–97.0) | ns      |
| C-reactive protein (mg/dL) | 35 (17–106)   | 41 (21–110)     | 27 (10–110)      | 49 (10–86)     | ns      |
| ESR (mm/h)             | 56 (25–82)    | 58 (30–83)      | 55 (23–78)       | 75 (27–94)     | ns      |

Mean ± standard deviation for normally distributed data or media (25th–75th percentiles) for sewed data.
Abbreviations: ESR, eritrosedimentation rate; CURB-65, Confusion, Urea, Respiratory rate, Blood pressure (age ≥65 years).

*Comparison between the 3 25OHD categories.

Despite a correlation between 25OHD and CURB-65, index (r = –.13; P = .049) was found, the CURB-65 showed no differences according to 25OHD levels and no differences in 25OHD levels were observed according to CURB-65 (low risk 0–1: 11.9 ± 7.5 ng/mL; intermediate/high risk 2–5: 11.6 ± 7.3 ng/mL).

A correlation between 25OHD and CCI (r = –.20, P = .007) and with the 10 years of life expectative (%) (r = .19; P = .008) was also observed. In addition, a higher CCI according to 25OHD category (<10, 10–20 and >20 ng/mL) levels (P = .05) were observed and higher 25OHD levels according to lower CCI (CCI 0 = 13.0 ± 8.2, CCI ≥ 1 = 10.5 ± 6.7 ng/mL; P = .0093) were also found.

4 | DISCUSSION

It is known that there is a high prevalence of vitamin D insufficiency and deficiency in adults and adolescents around the world. This is accentuated in the winter months and in high altitude areas. Here, we found only 1.8% with 25OHD > 30 ng/mL and a high prevalence of 25OHD deficiency (85%) among hospitalized adults with CAP. This could be explained...
in part by the CAP characteristics with a high prevalence in winter (54% in our study population). However, the CAP in summer-autumn also showed deficiency levels (16.1 ± 10.9 ng/mL). In addition, Lu et al. investigated the correlation between the level of 25OHD and CAP in elderly hospitalized patients and they found that patients hospitalized by CAP had lower 25OHD levels with respect to non-pneumonia group.

Serum 25OHD levels in women were lower than in men but no difference according BMI was observed our study. In addition, no correlation between 25OHD levels and BMI was found. Other authors described higher 25OHD levels with normal BMI than those with overweight and obesity. We also found that vitamin D deficiency is negatively associated with age. These findings were observed even in children with CAP. These patients with vitamin D deficiency had a significantly higher neutrophil percentage, but significantly lower lymphocyte percentage and hence vitamin D deficiency could affect the immune response in children with CAP. We did not find differences in the other biochemical determinations when the groups were stratified according to 25OHD levels.

In addition, no differences in X-ray and blood and sputum culture characteristics were found according to 25OHD levels. The microbiological rescue obtained in the blood culture was similar to that described in the literature as the used therapy.

Although in our study we had low number of complications, this may be because of the fact that high-risk patients were not included, as only hospitalized patients were considered in the general room.

When we analyzed the medical history, we found that patients with COPD had lower 25OHD levels respect other pathologies. Despite the small number of patients with 25OHD >20 ng/mL, this was previously reported by other authors.

Kim et al. found 80.4% vitamin D deficiency (<20 ng/mL) in patients hospitalized with CAP and serum vitamin D level was negatively associated with risk of 28-day mortality. Here, we showed similar percentage of 25OHD deficiency but the design of our study did not allow us to estimate mortality. A meta-analysis published 14 observational reports from January 2000 to March 2014 suggests that vitamin D deficiency increases susceptibility for severe infections and mortality of the critically ill. They found that 25OHD levels <20 ng/mL were associated with increased rates of infection (RR = 1.49), sepsis (RR = 1.46), 30-day mortality (RR = 1.42) and inhospital mortality (RR 1.79). In a subgroup analysis of adjusted data including vitamin D deficiency as a risk factor for 30-day mortality, the pooled RR was 1.76.

The different cutoff levels used by different studies are based on different study endpoints as fracture or osteoporosis and were done in the general population. Hence, the applicability of these cutoff levels in the critically ill is unclear because cutoff values perhaps are different in pleiotropic endpoints. Serum 25OHD concentration has been linked to mortality from all causes, cardiovascular diseases and respiratory diseases in different studies, but appropriate cutoffs to define risk categories are under debate.

The Pneumonia Severity Index (PSI) is used to classify 5 risk classes in the severity of a patient with pneumonia. Through this score, it can established that if the patients should be treated as outpatients or as hospitalized patients. But this index considers comorbidity neoplastic disease, liver disease, renal disease, congestive heart failure and cerebrovascular disease, giving a score to each of them. In our study, the 3 first comorbidities were considered as exclusion criteria because of their interference with vitamin D metabolism. For the reasons described, we did not use PSI in our study. Despite the knowledge that chronic kidney disease, chronic liver disease and neoplastic disease influence with the metabolism of vitamin D, many published studies did not exclude these important factors.

Remmelt et al. studied 272 hospitalized patients with CAP and they found vitamin D deficiency was associated with adverse outcome in CAP and that vitamin D status was an independent predictor of 30-day mortality and adds prognostic value to other biomarkers and prognostic scores in the PSI score.

In brief, CURB-65 index is 1 of the most frequently tools used for evaluating CAP-associated risk of mortality and clinical severity. As CCI is a method of classifying comorbidity and a valid method of estimating risk of death from comorbid disease. In our study, 25OHD levels correlated with CURB-65 score, Charlson comorbidity index (CCI) and with the 10 years of life expectative (%). Traditionally, biomarkers of infection for diagnostic and prognostic purposes have widely been used such as white blood cell count, CRP and eritrosedimentation rate but their prediction of risk in CAP is limited. We did not found correlation in either CRP or eritrosedimentation rate in our study.

5 CONCLUSIONS

It is concluded that hospitalized adults with CAP have a high percentage of severe deficiency of 25OHD levels and high CCI which could lead to higher CAP severity.

The knowledge of the characteristics of our population with CAP diagnosis is important for a better therapeutic approach.

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CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest with the contents of this article.

ETHICS
The study was approved by the Ethics Committee of School of Medicine, Rosario National University, Argentina. All participants gave their written informed consent.

AUTHOR CONTRIBUTIONS
All authors performed the study, collected and analyzed data. All authors read and approved the final manuscript. Designed study: MLB, JNM and LRB
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