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Association of Vitamin D Status with the Severity and Mortality of Community-Acquired Pneumonia in Iran during 2016-2017: A Prospective Cohort Study

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Abstract

Background: Community-acquired pneumonia (CAP) is a common disease considered as a major public health problem. It causes considerable morbidity and mortality despite antibiotic treatments. Hospital admission of CAP patients is a significant financial burden and many efforts are ongoing to decrease hospital stay durations. Vitamin D deficiency is associated with increased risk of respiratory infections. This study was designed to determine the association of vitamin D status with hospitalized CAP patient mortality and disease severity.

Methods: This prospective cohort study examined 180 CAP patients admitted to a teaching Hospital in Tehran, Iran during 2016-2017. Their demographic and anthropometric characteristics were recorded. The disease severity was evaluated based on CURB-65. Vitamin D status was determined by measuring by serum 25-hydroxylated vitamin D (25(OH)D) with ELISA. The patients were followed for 30 days to evaluate their vitality.

Results: One hundred and eighty pneumonia patients, including 104 males and 84 females, were recruited from respiratory disease, infectious disease, emergency, and ICU wards. Nearly 18% of the patients were current smokers. The CAP severity, evaluated by CURB-65, was determined to be non-severe in 74.4% of the patients. Patients were classified as vitamin D sufficient, insufficient, or deficient. Thirty percent of the patients were vitamin D sufficient, 18% were insufficient, and 52% were deficient. Thirty-day mortality was 40% (72 cases). Mortality was greater in males than in females (47.1% vs. 30.3%, p=0.03). The disease was significantly less severe in the patients who survived than in those who did not. The vitamin D status differed between males and females (p=0.027). The vitamin D status was lower in the more severe cases than in the less (p=0.036), and vitamin D deficiency was more prevalent in patients who died than in those who lived. Vitamin D concentration was negatively correlated with hospital stay duration. The 25(OH)D concentration was significantly greater in patients who survived than in those who did not (p<0.001).

Conclusions: Pneumonia severity and mortality risk were greater and hospital stays longer in vitamin D-deficient patients than in those with higher vitamin D status.

Keywords: Disease severity, Mortality, Pneumonia, Vitamin D.

Introduction

Pneumonia is a significant public health problem and one of the most common causes of admission in health centers (1), accounting for considerable morbidity and mortality despite the development and availability of new antibiotics (2, 3). Pneumonia and influenza combined are the eighth-leading

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causes of death in people over 65 in the United States and acute respiratory infections are the third-leading cause of death worldwide (3, 4), accounting for 4.26 million deaths in 2004, of which 98% were due to lower-respiratory tract-infections (5). In outpatients, community acquired pneumonia (CAP) mortality is less than 3%; however, in general ward-admitted patients the mortality reaches 5-10%, and can increase to 25% in intensive-care unit (ICU) patients (1). Although lower-respiratory-tract infections are the most common cause of mortality in low-income countries, pneumonia is the only infection among the ten leading causes of death in high-income countries (4). The mortality rate of pneumonia has not reduced considerably compared to decline achieved in mortalities due to other causes including infectious diseases like diarrhea, HIV and malaria (4). In 2015, lower-respiratory-tract infections caused 2.74 million deaths. Community-acquired pneumonia affects 4 million adults and causes 600,000 hospital admissions in the United States annually. The incidence of pneumonia is 1.5-14 cases per 1000 persons per year (6). The 30-day mortality from pneumonia ranged from 4-18% in hospitals and increases in the case of ICU admission (6). Old age is considered as a risk factor for mortality in pneumonia (7). The current pneumonia mortality has been estimated as 9733 cases for all ages in Iran, although the rate has been reduced 9.4% compared to that of 2005 (8). Generally the diagnosis of CAP is based on new lung infiltration in chest radiography with one of these criteria: fever over 38 ^{0}C or hypothermia, changes in lung sounds, or respiratory symptoms including cough, sputum, dyspnea, or pleuritic pain (9). The pneumonia severity index (PSI) and CURB-65 are two methods used to evaluate CAP severity. The sensitivity and specificity of CURB-65 are both 80%. This method classifies patients into low-, intermediate-, and high-risk groups (6). Vitamin D, a fat-soluble vitamin that behaves like a hormone, is produced in the skin from cholesterol by ultra-violet radiation. Although a few food items are vitamin D sources, these do not provide sufficient vitamin D for human needs. The main source of vitamin D is sunlight exposure (10). For vitamin D to be physiologically active it must be hydroxylated in two steps; first in the liver where it is hydroxylated to inactive 25(OH)D, and then in the kidney, where 25(OH)D is hydroxylated to 1,25(OH)D, the active form. However, 25(OH)D is considered as a marker for vitamin D status evaluation. The normal plasma concentration of 25(OH)D is 30 ng/ml or greater; concentrations of 20-30 ng/ml are considered as insufficient, and those below 20 ng/ml are considered deficient. The role of vitamin D in calcium absorption is well understood; however, recently its non-calcemic functions have been the subject of many studies (11). Vitamin D also contributes to immune system function; it increases immune system resistance against infections, strengthens native immunity, and increases the expression of antimicrobial peptides; consequently, its deficiency affects immunity and infection susceptibility. The active form of vitamin D may be produced locally by macrophages. The bactericidal capability of macrophages is decreased in vitamin D deficiency (12). Overall vitamin D contributes to bacteriostatic and bactericidal activities.

Considering age as a major risk factor for pneumonia incidence and mortality, their rates can be expected to increase in the future. Pneumonia mortality seems to be affected by nutrition. A few studies have attempted to determine a possible association between vitamin D status and pneumonia. Considering the role of vitamin D in immunity (13), it may contribute to pneumonia resistance. The aim of this study was to examine a possible association between vitamin D status and disease severity and mortality in CAP patients.

Materials and methods

This was a prospective cohort study of CAP patients who were admitted to a university hospital, in Tehran, Iran in 2016 and 2017. The patients were admitted to respiratory disease, infectious disease, emergency, and ICU wards. Patients were excluded if they were: taking vitamin D supplements during the past three months, receiving corticosteroid drugs, pregnant or lactating, or had chronic renal and/or liver diseases. A demographic questionnaire was completed by each study participant. Anthropometric measurements included age, sex, weight, height, and body mass index. Pneumonia severity was determined with CURB-65 (6). The patients were categorized into two groups; those with severe, and those with non-severe, disease.

To evaluate vitamin D status, venous blood was drawn from patients after an overnight fast. The patients were followed for 30 days to evaluate their vitality and survival.

Serum vitamin D concentration

To evaluate vitamin D status the concentration of plasma 25(OH)D was determined by ELISA (DIAsource Immunoassays SA, Louvain-la-Neuve, Belgium) according to the manufacturer's instructions. 25(OH)D concentrations of 30 ng/ml or greater were considered sufficient, 20-30 ng/ml were considered insufficient, and those below 20 ng/ml were considered deficient (14).

Statistical analyses

The quantitative data were reported as means and standard deviations. For nominal variables or categorical data, frequency and relative frequency were used. The normality of distribution of variables was evaluated by the Kolmogorov-Smirnov test. Student t-tests were used to compare quantitative data in two groups, and analysis of variance was used when more than two groups were compared. The Mann-Whitney test was used to compare two groups whenever the distribution was not normal. Chi-square or Fisher's exact tests were used to evaluate the association of two nominal variables. Log binomial regression analysis was used to evaluate the relative risk of predictors on the outcome measure of mortality. All analyses were performed using IBM SPSS version 24. The results were considered significant when the p value was less than 0.05.

Ethics statement

All the subjects were made aware of the protocol and purpose of the study. They completed and signed informed consent forms and were allowed to leave the project at any time. The study protocol was confirmed by the local ethical committee at the Tehran University of Medical Sciences (TUMS) (Ethical code: IR.TUMS.IKHC.REC.1395.640).

Results

Originally, 180 CAP patients were enrolled. The population was 57.8% male and 42.2% female. The mean age of the study group was 62.21 years with 60% of the patients over age 60. The age difference between males and females was significant (p=0.009, 59.47 vs. 65.96 years, independent t-test). The means and standard deviations of weight and body mass index for the patients were 66.72±12.82 and 24.54±4.02 kg/m^2, respectively. The weight difference between the two sexes was also significant (68.66 kg for males vs. 62.28 kg for females, p<0.001, Mann-Whitney test) while the prevalence of obesity or overweight between the sexes was not significant. At the time of the study, 18.3% of patients were current smokers. The characteristics of the study population are shown in Table 1.

Table 1. Characteristics of CAP patients≠

	Male (n=104)	Females (76)	p value
Age (years)	59.47±18.16	65.96±14.78	0.009*
Weight (kg)	68.66±11.42	62.28±9.09	<0.001$
BMI (kg/m^2)	24.27±3.33	24.32±3.34	0.92$
Smoking (%)	26.9	6.6	<0.001§

≠ mean±SD, BMI: Body Mass Index
* Two independent samples t-test
$ Mann-Whitney test
§ Chi-square test

Pneumonia severity was as rated as non-severe in 74.4% and severe in 25% of the subjects. The difference in severity state was not statistically significant between two sexes. The admission duration mean was 18.12 days with no difference between the two sexes.

The mean and SD of serum 25(OH)D concentration in the study population study were

24.62±18.34 ng/ml. Thirty percent of the patients were sufficient, 18% were insufficient, and 52% were deficient in vitamin D status.

Of the 180 CAP patients in the study, 40% died due to current illness. The mortality rate was greater in males than in females (47.1 vs. 30.3%, p=0.03, Chi-square test). The patients who survived were younger than those who died (59.97 vs. 65.5 yrs., p=031, two independent sample t-test). Most of the patients who died were over age 60. No difference in mortality was seen between the smoking and non-smoking groups and BMI had no effect on mortality (P=0.26, Mann-Whitney test). Although 58.3% of the patients who died had non-severe pneumonia, 67% of those who died were severe cases and 31% were non-severe. This difference was statistically significant (p<0.001). No significant difference in hospital stay duration was seen between patients who survived and those who died.

Vitamin D status was significantly greater in females than in males (29.49±22.03 ng/ml in females vs. 20.75±13.87 ng/ml in males, p=0.019, Mann-Whitney test). Vitamin D deficiency was more prevalent in patients over 60 than in those less than 60 (p=0.004, Chi-square test).

Of the patients who survived, the vitamin D concentration was significantly greater in the under-60 than in the over-60 group (p=0.046, spearman's rho=0.149). No significant difference in vitamin D status was seen between the obese and overweight vs. the normal-weight patients. But the sufficient status was more prevalent in patients with normal BMI in spite of statistically insignificancy. The hospitalization stay duration negatively correlated with 25(OH)D serum concentration. Patients with severe CAP had lower vitamin D concentrations than those with non-severe CAP (p=0.036). Although the hospital stay duration was longer for vitamin D-deficient patients than for non-vitamin D-deficient patients, this difference was not statistically significant (p=0.2). Vitamin D deficiency was significantly greater in patients who died than in those who survived (p<0.001, Chi-square test). Finally, vitamin D deficiency increased the risk of mortality (p=0.005, RR=2.39, 95% CI for Exp (B) 1.30-4.3). After controlling for age, BMI, sex, and pneumonia severity by multivariate analysis, the mortality risk was significantly greater in vitamin D-deficient patients than in the vitamin D-sufficient group (p=0.039, RR=1.95, 95% CI for Exp (B) 1.03-3.69).

Discussion

The rate of vitamin D deficiency in this study was similar to that reported in other studies conducted in Iran (15-22). Mamani et al. reported the prevalence of vitamin D deficiency and insufficiency at 81% (23). Vitamin D in the skin decreases with age (24). This physiological consequence of aging was shown in our study. Ramezani et al. (24) and Hovespian (25) reported the lowest vitamin D concentrations in the aged groups (25). It has been shown that the vitamin D is stored in adipose tissue, possibly resulting in vitamin D deficiency in obese individuals (26); therefore, we expected the deficiency status to be more prevalent in our obese patients, but no difference was seen.

The severe CAP patients in this study were in low vitamin D status. This finding is consistent with the study of Mamani et al. (23); however, Kim found no such association. This could be due to the different subject age groups of the two studies (27). The vitamin D concentration negatively correlated with the hospital stay duration, thus increasing the financial burden on health services.

Finally, this research demonstrates that mortality due to CAP is greater in males than in females, and also greater in older than in younger patients. We expected higher mortality rates in patients with severe than in those with non-severe pneumonia. We also found that the vitamin D state effects pneumonia severity. Mamani et al. showed vitamin D deficiency as a risk factor for mortality due to pneumonia (23). The mortality rate in this study was greater than that of previous ones; likely because our subjects were all hospital referrals. We conclude that the prevention of vitamin D deficiency might decrease the CAP mortality rate.

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