



ORIGINAL ARTICLE

## Vitamin D deficiency at pediatric intensive care admission<sup>☆</sup>

Corsino Rey<sup>a,\*</sup>, David Sánchez-Arango<sup>b</sup>, Jesús López-Herce<sup>c</sup>,  
Pablo Martínez-Cambor<sup>d</sup>, Irene García-Hernández<sup>e</sup>, Belén Prieto<sup>f</sup>, Zamir Pallavicini<sup>g</sup>

<sup>a</sup> Pediatric Intensive Care Unit, Hospital Universitario Central de Asturias, Universidad de Oviedo, Oviedo, Spain

<sup>b</sup> Pediatric Day Care Center of Culleredo and Complejo Hospitalario Universitario A Coruña, A Coruña, Spain

<sup>c</sup> Pediatric Intensive Care Department, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense de Madrid, Madrid, Spain

<sup>d</sup> Oficina de Investigación Biosanitaria FICYT, Universidad de Oviedo, Oviedo, Spain

<sup>e</sup> Pediatric Service, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain

<sup>f</sup> Biochemical Department, Hospital Universitario Central de Asturias, Universidad de Oviedo, Oviedo, Spain

<sup>g</sup> Pediatric Service, Hospital Universitario Central de Asturias, Oviedo, Spain

Received 22 April 2013; accepted 7 August 2013

Available online 30 October 2013

### KEYWORDS

25 hydroxivitamin D;  
Critically-ill children;  
Critical care;  
Prognostic markers;  
Mortality risk

### Abstract

**Objective:** to assess whether 25hydroxivitaminD or 25(OH)vitD deficiency has a high prevalence at pediatric intensive care unit (PICU) admission, and whether it is associated with increased prediction of mortality risk scores.

**Method:** prospective observational study comparing 25(OH)vitD levels measured in 156 patients during the 12 hours after critical care admission with the 25(OH)vitD levels of 289 healthy children. 25(OH)vitD levels were also compared between PICU patients with pediatric risk of mortality III (PRISM III) or pediatric index of mortality 2 (PIM 2) > p75 [(group A; n=33) vs. the others (group B; n=123)]. Vitamin D deficiency was defined as < 20 ng/mL levels.

**Results:** median (p25-p75) 25(OH)vitD level was 26.0 ng/mL (19.2-35.8) in PICU patients vs. 30.5 ng/mL (23.2-38.6) in healthy children (p=0.007). The prevalence of 25(OH)vitD < 20 ng/mL was 29.5% (95% CI: 22.0-37.0) vs. 15.6% (95% CI: 12.2-20.0) (p=0.01). Pediatric intensive care patients presented an odds ratio (OR) for hypovitaminosis D of 2.26 (CI 95%: 1.41-3.61). 25(OH)vitD levels were 25.4 ng/mL (CI 95%: 15.5-36.0) in group A vs. 26.6 ng/mL (CI 95%: 19.3-35.5) in group B (p=0.800).

**Conclusions:** hypovitaminosis D incidence was high in PICU patients. Hypovitaminosis D was not associated with higher prediction of risk mortality scores.

© 2013 Sociedade Brasileira de Pediatria. Published by Elsevier Editora Ltda. All rights reserved.

<sup>☆</sup> Please cite this article as: Rey C, Sánchez-Arango D, López-Herce J, Martínez-Cambor P, García-Hernández I, Prieto B, et al. Vitamin D deficiency at pediatric intensive care admission. J Pediatr (Rio J). 2014;90:135–42.

\* Corresponding author.

E-mail: [crey@uniovi.es](mailto:crey@uniovi.es) (C. Rey).

**PALAVRAS-CHAVE**

25-hidroxivitamina D;  
Crianças gravemente  
doentes;  
Terapia intensiva;  
Indicadores  
prognósticos;  
Risco de mortalidade

**Deficiência de vitamina D em internações na unidade de terapia intensiva pediátrica****Resumo**

**Objetivo:** avaliar se a deficiência da 25-hidroxivitamina D, ou 25 (OH) vitD, tem prevalência elevada em internações na unidade de terapia intensiva pediátrica, e se estaria relacionada à previsão de escores de risco de mortalidade.

**Método:** estudo observacional prospectivo comparando níveis de 25 (OH) vitD de 156 pacientes, mensurados nas primeiras 12 horas da internação em terapia intensiva, com níveis de 25 (OH) vitD de 289 crianças saudáveis. Os níveis de 25 (OH) vitD também foram comparados entre pacientes na UTIP com escore PRISM III ou PIM 2 > p75 (Grupo A; n = 33), e o restante, (Grupo B; n = 123). A deficiência de vitamina D foi definida como níveis < 20 ng/mL.

**Resultados:** o nível médio (p25-p75) de 25 (OH) vitD foi 26,0 ng/mL (19,2-35,8) em pacientes internados na UTIP, em comparação a 30,5 ng/mL (23,2-38,6) em crianças saudáveis (p = 0,007). A prevalência de 25 (OH) vitD < 20 ng/mL foi de 29,5% (IC 95%, 22,0-37,0), em comparação a 15,6% (IC 95%, 12,2-20,0) (p = 0,01). Os pacientes em terapia intensiva pediátrica apresentaram uma razão de chance (RC) para hipovitaminose D de 2,26 (IC 95%, 1,41-3,61). Os níveis de 25 (OH) vitD foram 25,4 ng/mL (IC 95%, 15,5-36,0) no grupo A, em comparação a 26,6 ng/mL (IC 95%, 19,3-35,5) no grupo B (p = 0,800).

**Conclusões:** a incidência de hipovitaminose D foi elevada em pacientes em terapia intensiva pediátrica, mas não foi associada à maior previsão de escores de risco de mortalidade.

© 2013 Sociedade Brasileira de Pediatria. Publicado por Elsevier Editora Ltda. Todos os direitos reservados.

**Introduction**

Low levels of vitamin D are common in adult and pediatric populations.<sup>1</sup> Vitamin D deficiency has been classically related with osseous illness, such as rickets. Currently, vitamin D deficiency is considered to be related with overall mortality,<sup>2</sup> prevention of infections, innate immunity,<sup>3</sup> hypertension,<sup>4</sup> hypertriglyceridemia, type 1 and 2 diabetes mellitus,<sup>5</sup> neoplasms,<sup>6</sup> and autoimmune disorders.<sup>7</sup> In children, it has been related to severe asthma, bronchiolitis episodes, and lower response to corticoids.<sup>8</sup>

The most important source of vitamin D is the skin, through the action of ultraviolet B radiation on 7dehydrocholesterol. Vitamin D must be metabolized to 25 hydroxvitamin D (25(OH)vitD) in the liver, which is an inactive precursor with a half-life of approximately two to three weeks. The half-life of the active form (1,25(OH)vitD) is only four to 24 hours.<sup>9</sup> For that reason, 25 (OH)vitD has been the most common form of vitamin D measured in previous studies<sup>10</sup> In healthy children, age, skin pigmentation, season of the year, sun exposure, and dietary calcium intake influence 25(OH)vitD concentrations. Most studies have adopted the definition of vitamin D insufficiency as 25(OH)vitD concentrations lower than 30 ng/mL, and vitamin D deficiency as concentrations below 20 ng/mL.<sup>10</sup>

Recently, vitamin D deficiency has been associated with higher illness severity upon admission, mortality, and worse short and long term outcomes in adult intensive care units (ICU) patients.<sup>11-13</sup> Several studies<sup>14-16</sup> provided new information regarding the relationship between vitamin D status and critical illnesses in children admitted to pediatric ICUs (PICUs). It was observed that hypovitaminosis D is a common finding in critically-ill children. McNally et al.<sup>16</sup> also reported that vitamin D deficiency was associated with greater severity of critical illness. However, Rippel et al.<sup>14</sup> did not find an

association between hypovitaminosis D and length of stay or hospital survival. Vitamin D status may play an important role in acute stress and critical illness, but its pleiotropic effects in acute illness are not completely understood. Many confounding factors (hemodilution, interstitial extravasation, decreased synthesis of binding proteins, renal wasting of 25(OH)vitD, pH, underlying disease, season of the year, age, and dietary supplementation, among others) influence vitamin D status during critical illness.<sup>17</sup> To date, there is no consensus regarding the optimal definitions of vitamin D deficiency, nor the threshold levels to define health benefits.<sup>17,18</sup>

Therefore, this study aimed to investigate whether vitamin D deficiency is highly prevalent in patients admitted to a PICU. The secondary objective was to verify whether vitamin D deficiency would be associated with increased mortality risk scores and illness severity at PICU admission.

**Patients and methods**

This study was a secondary analysis of data and biological samples collected as part of the new prognosis biomarkers investigation, a prospective observational study set in the eight-bed PICU of the Hospital Universitario Central de Asturias, in Oviedo, Spain. The study protocol was approved by the Hospital Ethics Committee. The study was conducted in 156 patients admitted to the PICU and aged less than 16 years. The exclusion criteria were no blood extraction during the first 12 hours after admission; lack of consent to participate by parents or by children older than 12 years; known or suspected adrenal, pituitary, or hypothalamic disease; and use of systemic steroids for > ten days in the previous month, or more than one dose of systemic steroids within 24 hours of admission (except for dexamethasone).

On every blood test sampled in the first 12 hours after admission, the following variables were recorded: age, weight, underlying disease, and diagnosis. Respiratory rate, heart rate, blood pressure, O<sub>2</sub> saturation, urine rate, and administration of vasopressor agents were recorded hourly. Radiographic and microbiologic diagnostics were performed when indicated. Blood cultures were performed when there was clinical suspicion of infection or when the patient's temperature was > 38°C. The pediatric index of mortality 2 (PIM 2) value was calculated at admission, and the pediatric risk of mortality III (PRISM III) value was calculated during the first 12 h after admission, as it was the normal clinical practice. Routine biochemical assays, including C-reactive protein (CRP) and procalcitonin (PCT), were performed during the first 12 hours after admission. Venous blood samples were collected in tubes containing ethylenediamine-tetra-acetic acid (EDTA). A plasma aliquot was frozen and stored at -80°C for further determination of 25(OH)vitD, mid-regional pro-adrenomedullin (MR-proADM), and carboxy-terminal pro-endothelin-1 (CT-proET-1).

### Healthy children

The 25(OH)vitD levels of the PICU patients were compared with the 25(OH)vitD levels that were obtained as part of a study on vitamin D status that is currently under development in a population of healthy children from the city of Oviedo (Asturias, Spain). Data from 289 healthy children were obtained.

### Definition of hypovitaminosis D

Vitamin D deficiency was defined as < 20 ng/mL 25(OH)vitD levels.<sup>10</sup>

### Mortality risk groups

Patients were divided in two groups according to mortality risk scores. Higher risk mortality group (group A) included patients with a PIM 2 or PRISM III score > p75 (n = 33); lower risk mortality group (group B) comprised the remaining patients (n = 123).

### Measurement of 25(OH)vitD, CRP, PCT, MR-proADM, and CT-proET-1

Serum 25(OH)vitD was measured using a direct competitive chemiluminescence immunoassay (LIAISON® Analyzer). The assay range is 4.0 to 150 ng/mL. Plasma CRP was measured on a Modular Analytics Cobacs 6000 (Roche Diagnostics - IN, USA) using an immunoturbidimetric technique. The analytical detection limit was 0.07 mg/dL.

MR-proADM, CT-proET-1, and PCT were measured in EDTA plasma using a sandwich immunoassay (TRACE technology; Brahms - Hennigsdorf, Germany). Analytical detection limits were 0.08 nmol/L for pro-ADM, 0.4 pmol/L for CT-proET-1, and 0.02 ng/mL for PCT.

### Statistical analysis

Patients' clinical and biological parameters were described using frequencies, percentages, means, medians, and ranges (p25-p75). Groups of patients were compared using the Mann-Whitney U-test for continuous variables, and cross tables and exact chi-squared test were used for categorical data. Adjusted odds ratios (OR) were estimated by multivariate logistic regression analysis (step-forward criteria including all relevant likelihood ratio based variables). A p-value < 0.05 was considered as statistically significant.

## Results

### Baseline characteristics

This study comprised 156 PICU patients. Baseline demographic, clinical, and laboratory characteristics of the PICU patients are shown in Table 1. The main reasons for PICU admission were postoperative and respiratory and infectious disease. Seventy-six patients (48.7%) were younger than 4 years.

### Hypovitaminosis D incidence

Demographic and vitamin D data in the PICU population and healthy children are reported in Table 1. 25(OH)vitD levels were lower and the incidence of hypovitaminosis D was higher in the PICU population. Vitamin D values in critically ill children had a negative correlation with patient's age (Spearman's correlation coefficient: -0.421; p < 0.001). Therefore, vitamin D deficiency was compared between healthy and PICU children in different age groups (Table 2). The incidence of vitamin D deficiency increased with age in both groups of patients. PICU patients had a crude OR for hypovitaminosis D of 2.26 (CI 95%: 1.41-3.61). The age, weight, and gender-adjusted OR was 1.83 (CI 95%: 1.10-3.06).

Median (p25-p75) 25(OH)vitD levels during the different seasons of the year in PICU patients were: spring, 30.1 ng/mL (18.2-36.5); summer, 28.1 ng/mL (20.5-33.3); fall, 24.9 ng/mL (19.6-39.0); and winter, 23.0 ng/mL (15.4-38.0), p = 0.761.

Baseline demographic, clinical, and laboratory characteristics of the PICU vitamin D deficient group vs. the remainder of the PICU sample are shown in Table 3. Vitamin D deficient patients were older and heavier. PICU stay, inotropic support, and need for mechanical ventilation and non-invasive ventilation showed no difference between both groups. Respiratory diagnosis at admission was less frequent in vitamin D deficient patients, whereas metabolic-renal diagnosis was more common. Underlying disease incidence was higher in hypovitaminosis D patients (47.8% vs. 36.3%; p = 0.132 (Table 3). Median (p25-p75) 25(OH)vitD levels were 23.4 ng/mL (18.6-33.3) in patients with underlying disease (n = 62) vs. 30.1 ng/mL (20.0-39.3) in patients without underlying disease (n = 94); (p = 0.039).

**Table 1** Demographic and vitamin D data in healthy children and in PICU population (median, p25-p75).

Demographic and vitamin D data	Healthy children (n = 289)	PICU population (n = 156)	p-value
Age at admission (months)	36.0 (24.0-84.0)	46.0 (15.2-116.7)	0.678
Weight (kg)	16.5 (12.0-28.0)	16.0 (11.0-33.0)	0.120
Gender, male, n (%)	166 (57.4)	93 (59.6)	0.836
25(OH)vitD (ng/mL)	30.5 (23.2-38.6)	26.0 (19.2-35.8)	0.007
25(OH)vit D < 20 ng/mL (%)	15.6% (95% CI: 12.2-20.0)	29.5% (95% CI: 22.0-37.0)	0.01

CI, confidence interval; PICU, pediatric intensive care unit; 25 (OH)vitD, 25 hydroxvitamin D.

## Risk of mortality

Baseline demographic, clinical, and laboratory characteristics of the patients with higher risk of mortality (group A) vs. the rest of the sample are shown in Table 4. Group A patients were younger and lighter. PICU stay, inotropic support, and need for mechanical ventilation and non-invasive ventilation were higher in group A. Postoperative diagnosis at admission was less frequent in group A, whereas respiratory diagnosis was more frequent. PCT, MR-proADM, and CT-proET-1 plasma levels were significantly higher in patients with higher prediction of mortality risk scores, whereas CRP and 25OH(vitD) levels were no different between groups A and B.

Additional evaluation using a multivariate logistic regression analysis found an adjusted OR by age, season, and underlying disease of 2.42 (95% CI: 0.86-6.84) for vitamin D deficiency and prediction of mortality risk scores ( $p = 0.09$ ).

## Discussion

This study demonstrated that, in a sample of critically ill children from the north of Spain, the prevalence of hypovitaminosis D was high at PICU admission. The present study supports recent investigations<sup>14-16</sup> showing that hypovitaminosis D is common in critically ill children. It was observed that 29.5% of the present PICU patients had 25(OH)vitD < 20 ng/mL, similar to the rate of 34.5% from the study by Rippe et al.<sup>14</sup> in a cohort of critically ill Australian children, and lower than the 40.1% and 69% reported by Madden et al.<sup>15</sup> and by McNally et al.<sup>16</sup> in North American and Canadian children, respectively.

The 25(OH)vitD levels from the present PICU patients were compared with the 25(OH)vitD levels that were obtained as part of a study on vitamin D status that is currently under development in a population of healthy children from the city of Oviedo (Asturias, Spain). The prevalence of vitamin D deficiency in Oviedo's population of healthy children was similar to the reported prevalence of 18% in Mansbach's population-based study of healthy North American children,<sup>19</sup> but lower than the published prevalence of vitamin D deficiency in North American and Australian adolescents, which ranged from 29% to 68%.<sup>20,21</sup> The explanation for these differences is the age. A previously described inverse correlation between 25(OH)vitD levels and age was confirmed by the present study. The median age of the present healthy children cohort was 3 years, much younger than the adolescent sample from the United States and Australia. The incidence of vitamin D deficiency was compared between healthy and PICU children in different age groups (Table 2). As expected, incidence of vitamin D deficiency increased with age in both group of patients. PICU patients had double incidence of hypovitaminosis D in all age groups, but the differences were clearly statistically significant in the older age group, and were almost significant in the medium age group. The probable reason is that the fragmentation of the sample produced a small sample size in the younger age group. Regarding the season of the year, there were no significant differences in 25(OH)vitD levels in the present study, although values tended to be lower in fall and winter, which agree with previous studies performed in the North of Spain<sup>18</sup> and in other countries.<sup>20</sup> In healthy children, factors consistently associated with 25(OH)vitD levels were age, season of the year, and dietary calcium intake.<sup>22</sup>

**Table 2** Vitamin D deficiency (25(OH)vit D < 20 ng/mL) in healthy and PICU children in different age groups.

Age group	Healthy children (n = 289)	PICU children (n = 156)	p-value
< 1 year	(n = 46) 6.5% (95% CI: 1.4-17.9)	(n = 28) 11.1% (95% CI: 2.4-29.2)	0.664
1-5 years	(n = 156) 12.8% (95% CI: 7.3-18.4)	(n = 61) 23.3% (95% CI: 11.8-34.9)	0.064
> 5 years	(n = 87) 26.2% (95% CI: 16.2-36.2)	(n = 67) 43.1% (95% CI: 30.3-55.9)	0.036

CI, confidence interval; PICU, pediatric intensive care unit; 25 (OH)vitD, 25 hydroxvitamin D.

**Table 3** Demographic, clinical, and laboratory data in the overall PICU population and in patients with and without vitamin D deficiency.

	25(OH)vitD < 20 ng/mL n = 46	25(OH)vitD ≥ 20 ng/mL n = 110	p-value	Overall PICU population n = 156
<i>Demographic and clinical characteristics</i>				
Age at admission (months)	97.0 (44.5-145.0)	34.0 (14.0-98.0)	< 0.001	46.0 (15.2-116.7)
Weight (kg)	23.0 (14.9-44.8)	14.4 (10.0-30.0)	< 0.001	16.0 (11.0-33.0)
Gender, Male, n (%)	28 (60.9)	65 (59.1)	0.860	93 (59.6)
PICU stay (days)	3.0 (1.0-5.0)	4.5 (2.0-7.0)	0.067	4.0 (2.0-6.0)
Mechanical ventilation, n (%)	18 (39.1)	45 (40.9)	0.860	63 (40.4)
Non-invasive ventilation, n (%)	7 (17.1)	16 (24.5)	0.385	33 (15.8)
Inotropic/vasopressor support, n (%)	6 (13.0)	7 (6.4)	0.205	13 (8.3)
<i>Admission diagnosis</i>				
Postoperative	15 (33)	32 (29)	0.806	47
Respiratory	5 (10)	30 (27)	0.042	35
Infectious	6 (13)	18 (16)	0.779	24
Traumatic	2 (4)	11 (10)	0.397	13
Neurologic	1 (2)	7 (6)	0.494	8
Metabolic-renal	7 (15)	2 (2)	0.004	9
Others	10 (22)	10 (9)	0.058	20
PRISM III, absolute value	3.71 ± 3.86	3.34 ± 4.67	0.629	3.4 (4.4)
PIM 2, %	1.13 ± 1.20	2.99 ± 10.86	0.086	2.5 (9.3)
Underlying disease, n (%)	22 (47.8)	40 (36.3)	0.132	62 (39.7)
<i>Laboratory data</i>				
pH	7.3 (7.2-7.4)	7.3 (7.3-7.4)	0.625	7.3 (7.3-7.4)
Bicarbonate (mEq/L)	21.9 (18.7-24.2)	21.8 (19.9-23.5)	0.769	21.8 (19.7-23.7)
Lactate (mmol/L)	1.4 (0.9-1.8)	1.3 (0.8-2.0)	0.647	1.3 (0.9-2.0)
Platelets (X1000/mm <sup>3</sup> )	246 (185-296)	292 (214-388)	0.017	273 (200-365)

CI, confidence interval; PICU, pediatric intensive care unit; PIM 2, pediatric index of mortality 2; PRISM III, pediatric risk of mortality III; 25 (OH)vitD, 25 hydroxi vitamin D.

PRISM III and PIM 2 are expressed as mean ± standard deviation, admission diagnosis as absolute value and %, and the remaining variables as median (P25-P75).

Unfortunately, data regarding children's calcium intake was not available.

Regarding admission diagnosis, a lower respiratory diagnosis rate was observed in patients with vitamin D deficiency. In the few published pediatric studies,<sup>23</sup> an association was found between vitamin D deficiency and lung function, as well as with the risk for upper respiratory tract infections. A higher metabolic-renal diagnosis rate in patients with vitamin D deficiency was also observed. Metabolic-renal diseases can negatively influence the vitamin D metabolic pathways, affecting 25(OH)vitD levels.<sup>17</sup>

In the present sample, patients with underlying disease had lower levels of 25(OH)vitD. These patients are at a higher risk for reduced vitamin D levels through abnormal diets, altered metabolism, or reduced environmental exposure.

### Risk of mortality

Vitamin D deficiency has recently been shown to be associated with mortality in critically ill adults.<sup>11-13,24,25</sup> Other recent investigations have not observed this relationship.<sup>26,27</sup> Considering that the present study was not sufficiently powered to observe differences in survival,

other surrogate markers of PICU outcome were used, such as mortality scores. In accordance with Rippel et al.,<sup>14</sup> no associations were observed between vitamin D status and predicted PRISM III and PIM 2 mortality. However, Madden et al.<sup>15</sup> and McNally et al.<sup>16</sup> demonstrated that 25(OH)vit D levels at admission were inversely associated with PRISM III in North American children. Furthermore, duration of mechanical or non-invasive ventilation and length of PICU stay did not show differences between low and normal 25(OH)vitD groups in the present sample, in agreement with the data observed by Rippel et al.<sup>14</sup> in Australian children. However, McNally et al.<sup>16</sup> found an association of vitamin D deficiency with longer length of stay. Geographic and ethnic differences, as well as different causes of PICU admissions, could explain the similar results in the present study and in the Australian study, and the differences with both North American studies. Variations in patient responses to acute stress and critical illness may depend on the degree of vitamin D insufficiency and the patient's tissue requirements.<sup>17</sup>

Other prognostic markers, such PCT, MR-proADM, and CT-proET-1 were associated with risk of mortality (Table 2). Therefore, these biomarkers would have more utility than 25(OH)vitD to establish the risk of mortality in critically ill children.

**Table 4** Demographic, clinical, laboratory data, and marker levels in patients with higher vs. lower prediction of risk mortality scores.

	Group A (PRISM III or PIM 2 > p75) (n = 33)	Group B (PRISM III and PIM 2 ≤ p75) (n = 123)	p-value
<i>Demographic and clinical characteristics</i>			
Age at admission (months)	21.0 (8.2-56.0)	58.5 (23.2-123.5)	0.007
Weight (kg)	11.1 (8.8-20.2)	17.2 (12.0-35.4)	0.012
Gender, male, n (%)	22 (66.7)	71 (57.7)	0.426
PICU stay (days)	5.0(3.0-9.5)	3.0 (2.0- 6.0)	0.008
Mechanical ventilation, n (%)	25 (75.8)	38 (30.9)	< 0.001
Non-invasive ventilation, n (%)	15 (45.5)	18 (22.4)	0.001
Inotropic/vasopressor support, n (%)	9 (27.3)	4 (3.3)	<0.001
<i>Admission diagnosis</i>			
Postoperative	1 (3)	46 (37)	< 0.001
Respiratory	12 (36)	23 (19)	0.054
Infectious	6 (18)	18 (15)	0.818
Traumatic	3 (9)	10 (8)	0.859
Neurologic	3 (9)	5 (4)	0.473
Metabolic-renal	4 (12)	5 (4)	0.179
Others	4 (12)	16 (13)	0.875
PRISM III, absolute value	8.0 ± 6.7	2.2 ± 2.3	< 0.001
PIM 2, %	8.6 ± 18.4	0.68 ± 0.46	0.019
<i>Laboratory data</i>			
pH	7.3 (7.2-7.4)	7.4 (7.3-7.4)	0.012
Bicarbonate (mEq/L)	21.8 (16.6-24.1)	21.8 (19.9-23.7)	0.898
Lactate (mmol/L)	1.4 (0.97-2.1)	1.2 (0.80-2.0)	0.319
Platelets (x 1,000/mm <sup>3</sup> )	244 (163-409)	281 (214-364)	0.277
<i>Markers</i>			
CRP (mg/dL)	2.58 (0.50-14.9)	1.05 (0.10-8.4)	0.123
PCT (ng/mL)	1.4 (0.3-10.4)	0.18 (0.07-1.3)	< 0.001
MR-proADM (nmol/L)	0.79 (0.49-1.5)	0.46 (0.33-0.60)	< 0.001
CT-proET-1 (pmol/L)	80.7 (57.6-115.9)	50.7 (35.8-75.7)	< 0.001
25(OH)vitD (ng/mL)	25.40 (15.5-36.0)	26.6 (19.3-35.5)	0.800
25(OH)vit D < 20 ng/mL, n (%)	11 (33.3%)	37 (30.1%)	0.832

CRP, C-reactive protein; CT-proET-1, carboxy-terminal pro-endothelin-1; MR-proADM, mid-regional pro-adrenomedullin; PCT, procalcitonin; PICU, pediatric intensive care units; PIM 2, pediatric index of mortality 2; PRISM III, pediatric risk of mortality III; 25 (OH)vitD, 25 hydroxivitamin D.

PRISM III and PIM 2 were expressed as mean ± standard deviation, admission diagnosis as absolute value; the other variables were expressed as median (P75-P25).

By regulating the expression of more than 200 genes, including those influencing cell growth, 1,25-dihydroxyvitamin D<sub>3</sub> plays an important role in the proliferation, maturation, and death of cells. The identification of modifiable risk factors could help to guide new preventative or therapeutic strategies for pediatric critical illness. However, recent evidence<sup>17</sup> suggests that the interpretation of vitamin D status based on 25(OH)vitD levels in acute illness should be performed with caution. Significant variation in 25(OH)vitD levels may occur from hour to hour in acutely ill patients, and single point assessment may be inaccurate in certain cases. Moreover, vitamin D deficiency would not only be dependent on the severity of vitamin D depletion, but would also be related to tissue requirement.<sup>28</sup> Therefore new studies are necessary in order to determine reliable markers of vitamin D status in the acute care setting, as well as strategies to confirm whether vitamin D

supplementation is useful for hypovitaminosis D in critically ill children.

The present study has limitations. Firstly, parathyroid hormone (PTH) was not measured. The diagnosis of vitamin D deficiency usually requires the association of serum 25(OH)vitD levels lower than 20ng/mL and elevated serum PTH concentrations.<sup>29</sup> Secondly, the relatively small sample size and the low mortality limited the capacity to analyze specific subgroup of patients. Thirdly, the original study was not intended to estimate the prevalence of vitamin D deficiency; therefore, a specific questionnaire about dietary habits, vitamin D supplementation, or sun exposure was not performed. Finally, 25(OH)vitD levels were analyzed during the first 12 hours after PICU admission; evolution of 25(OH)vitD levels during the first days of admission would have higher accuracy.

In conclusion, in a population of children from the North of Spain, hypovitaminosis D incidence was high at PICU admission. To the authors' knowledge, this is the first prospective study comparing 25(OH)vitD levels in critically ill patients with healthy children population from the same area. Hypovitaminosis D was not associated with higher prediction of mortality risk scores, length of stay, and inotropic or respiratory support. Further studies are required to identify reliable markers of vitamin D status in the acute care setting, as well as strategies to confirm whether vitamin D supplementation could be useful in critically ill children with hypovitaminosis D.

## Funding

This study was partly funded by a grant from "Fundación Ernesto Sánchez Villares". Pablo Martínez-Cambor was supported by the Grant MTM2011-23204 of the Spanish Ministry of Science and Innovation (FEDER support included).

## Conflicts of interest

Corsino Rey had received speaker honoraria from Brahms Company to attend meetings related to sepsis biomarkers. The remaining authors declare no conflicts of interest. Fundación Ernesto Sánchez Villares, Spanish Ministry of Science and Innovation, and Brahms Company had no participation in the development of the manuscript, including study design, collection analysis, interpretation of data, writing of the report, nor the decision to submit the paper for publication.

## Acknowledgements

The authors would like to thank the children and parents who participated in this study. The authors also acknowledge the assistance of the PICU medical and nursing staff of Hospital Universitario Central de Asturias.

## References

- Pearce SH, Cheetham TD. Diagnosis and management of vitamin D deficiency. *BMJ*. 2010;340:b5664.
- Ford ES, Zhao G, Tsai J, Li C. Vitamin D and all-cause mortality among adults in USA: findings from the National Health and Nutrition Examination Survey Linked Mortality Study. *Int J Epidemiol*. 2011;40:998–1005.
- Adams JS, Ren S, Liu PT, Chun RF, Lagishetty V, Gombart AF, et al. Vitamin D-directed rheostatic regulation of monocyte antibacterial responses. *J Immunol*. 2009;182:4289–95.
- Pilz S, Tomaschitz A. Role of vitamin D in arterial hypertension. *Expert Rev Cardiovasc Ther*. 2010;8:1599–608.
- Mitri J, Muraru MD, Pittas AG. Vitamin D and type 2 diabetes: a systematic review. *Eur J Clin Nutr*. 2011;65:1005–15.
- Manson JE, Mayne ST, Clinton SK. Vitamin D and prevention of cancer-ready for prime time? *N Engl J Med*. 2011;364:1385–7.
- Kriegel MA, Manson JE, Costenbader KH. Does vitamin D affect risk of developing autoimmune disease? asystematic review. *Semin Arthritis Rheum*. 2011;40:512–31.e8.
- Searing DA, Zhang Y, Murphy JR, Hauk PJ, Goleva E, Leung DY. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. *J Allergy Clin Immunol*. 2010;125:995–1000.
- Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics*. 2008;122:398–417.
- Hollis BW, Wagner CL, Drezner MK, Binkley NC. Circulating vitamin D3 and 25-hydroxyvitamin D in humans: an important tool to define adequate nutritional vitamin D status. *J Steroid Biochem Mol Biol*. 2007;103:631–4.
- Venkatram S, Chilimuri S, Adrish M, Salako A, Patel M, Diaz-Fuentes G. Vitamin D deficiency is associated with mortality in the medical intensive care unit. *Crit Care*. 2011;15:R292.
- Braun A, Chang D, Mahadevappa K, Gibbons FK, Liu Y, Giovannucci E, et al. Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill. *Crit Care Med*. 2011;39:671–7.
- Braun AB, Gibbons FK, Litonjua AA, Giovannucci E, Christopher KB. Low serum 25-hydroxyvitamin D at critical care initiation is associated with increased mortality. *Crit Care Med*. 2012;40:63–72.
- Rippel C, South M, Butt WW, Shekerdemian LS. Vitamin D status in critically ill children. *Intensive Care Med*. 2012;38:2055–62.
- Madden K, Feldman HA, Smith EM, Gordon CM, Keistling SM, Sullivan RM, et al. Vitamin D deficiency in critically ill children. *Pediatrics*. 2012;130:421–8.
- McNally JD, Menon K, Chakraborty P, Fisher L, Williams KA, Al-Dirbashi OY, et al. The association of vitamin D status with pediatric critical illness. *Pediatrics*. 2012;130:429–36.
- Quraishi SA, Camargo Jr CA. Vitamin D in acute stress and critical illness. *Curr Opin Clin Nutr Metab Care*. 2012;15:625–34.
- Alonso A, Rodríguez J, Carvajal I, Prieto MA, Rodríguez RM, Pérez AM, et al. Prophylactic vitamin D in healthy infants: assessing the need. *Metabolism*. 2011;60:1719–25.
- Mansbach JM, Ginde AA, Camargo Jr CA. Serum 25-hydroxyvitamin D levels among US children aged 1 to 11 years: do children need more vitamin D? *Pediatrics*. 2009;124:1404–10.
- Dong Y, Pollock N, Stallmann-Jorgensen IS, Gutin B, Lan L, Chen TC, et al. Low 25-hydroxyvitamin D levels in adolescents: race, season, adiposity, physical activity, and fitness. *Pediatrics*. 2010;125:1104–11.
- Rovner AJ, O'Brien KO. Hypovitaminosis D among healthy children in the United States: a review of the current evidence. *Arch Pediatr Adolesc Med*. 2008;162:513–9.
- Gordon CM, Feldman HA, Sinclair L, Williams AL, Kleinman PK, Perez-Rossello J, et al. Prevalence of vitamin D deficiency among healthy infants and toddlers. *Arch Pediatr Adolesc Med*. 2008;162:505–12.
- Weiss ST. Asthma in early life: is the hygiene hypothesis correct? *J Pediatr (Rio J)*. 2008;84:475–6.
- Lee P, Eisman JA, Center JR. Vitamin D deficiency in critically ill patients. *N Engl J Med*. 2009;360:1912–4.
- Lee P, Nair P, Eisman JA, Center JR. Vitamin D deficiency in the intensive care unit: an invisible accomplice to morbidity and mortality? *Intensive Care Med*. 2009;35:2028–32.
- Lucidarme O, Messai E, Mazzoni T, Arcade M, du Cheyron D. Incidence and risk factors of vitamin D deficiency in critically ill patients: results from a prospective observational study. *Intensive Care Med*. 2010;36:1609–11.
- Cecchi A, Bonizzoli M, Douar S, Mangini M, Paladini S, Gazzini B, et al. Vitamin D deficiency in septic patients at ICU admission is not a mortality predictor. *Minerva Anestesiol*. 2011;77:1184–9.

28. Venkatesh B, Davidson B, Robinson K, Pascoe R, Appleton C, Jones M. Do random estimations of vitamin D3 and parathyroid hormone reflect the 24-h profile in the critically ill? *Intensive Care Med.* 2012;38:177–9.
29. Abrams SA, Griffin IJ, Hawthorne KM, Gunn SK, Gundberg CM, Carpenter TO. Relationships among vitamin D levels, parathyroid hormone, and calcium absorption in young adolescents. *J Clin Endocrinol Metab.* 2005;90:5576–81.