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Correlation of vitamin D deficiency with mortality in critically ill patients admitted to the intensive care unit.

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ABSTRACT

INTRODUCTION: Vitamin D, which is a fat-soluble vitamin, plays a key role in enhancing the intestinal absorption of calcium, magnesium and phosphate. In severely ill patients, vitamin D can adversely affect immune and metabolic functions, contributing to poorer outcomes. The aim of this study was to correlate vitamin D with mortality in critically ill patients.

MATERIALS AND METHODS: A prospective observational study was conducted, involving 162 patients in an intensive care unit (ICU). 162 patients were divided into two groups according to vitamin D Deficiency Group levels ≤ 20 ng/ml and Non vitamin D deficiency group levels <20 ng / ml and non-vitamin D deficiency group B levels > 20ng/ml. Data collected during the study included the APACHE II (acute physiology and chronic health evaluation) score at ICU admission, SOFA (sequential organ failure assessment) scores throughout the ICU stay, the need for mechanical ventilation, inotropic support, length of stay in ICU, and ICU outcomes, which were classified as either discharge or mortality.

RESULTS: Of the 162 patient admitted to ICU, the prevalence of vitamin D deficiency in this study was 140 (86.4%) and nondeficient 22 (13.6%). The mortality rate in the vitamin D deficient group was 40% compared to 18.18% in the non-deficient group. The difference in mortality in both groups for mortality was statistically significant (p-value < 0.05). Vitamin D deficiency was not associated as an independent risk factor for ICU mortality [Odds ratio (OR) 1.220, 95% CI (0.825-1.805) (p-value -0.320)].

CONCLUSIONS: The vitamin D-deficient group had a significantly higher mortality rate compared to the patient in the non-deficient group. But vitamin D deficiency was not found to be an independent risk factor for mortality.

KEY WORDS: Intensive care unit, mortality, vitamin D.

INTRODUCTION

Vitamin D is a fat-soluble vitamin that plays a role in increasing intestinal absorption of calcium, magnesium, and phosphate [1]. About 90 % of vitamin D needs are met with adequate exposure while dietary sources contribute only to the remaining 10 % of the daily requirement [2]. The role of vitamin D as pleiotropic hormone is primarily involved in calcium haemostasis and acts as an essential factor involved in different immune modulations and also plays a key role in several pathways of the innate immune response system, controlling cell growth, differentiation, and apoptosis besides skeletal and muscle development, and is also required for cardiovascular and central nervous system functioning [2,3].

It is said that any critically ill patient has affected the internal environment of the body and may disturb the reserves of vital nutrients and minerals of the body. Nutrition is usually inadequate in these patients, and this may further aggravate any deficiencies. Vitamin D deficiency may hinder immune and metabolic functions in severely ill patients, leading to worse outcomes [4,5]. Other important roles for vitamin D have been determined, such as affecting cell growth, proliferation, apoptosis and modulating the innate and adaptive immune response to infectious pathogens along with anti-inflammatory properties [6]. Vitamin D deficiency decreases the production of the antimicrobial peptide Cathelicidin, which increases the susceptibility to viruses and bacteria [7,8], and influences cytokine profiles through the immune system (innate and adaptive) and the NFκB (nuclear factor kappa light chain enhancer of activated B cells) pathway [9,10]. Therefore, vitamin D deficiency may lead to a pro-inflammatory state and increase the severity of the disease, which leads to multi-organ failure [11].

The most widely used are the Clinical Practice Guidelines of the Endocrine Society that define vitamin D deficiency as a serum level below 20 ng/ml (50 nmol/l), vitamin D insufficiency as 20–30 ng/ml (50–75 nmol/l) and a normal vitamin D status above 30 ng/ml (75 nmol/l) [11,12]. The prevalence of vitamin D deficiency in intensive care patients has been reported to range from 26% to 82% [4,13]. The individual's vitamin D status depends on a variety of factors including age, skin pigmentation, clothing, genetic factors, nutrition, seasonality, latitude, sea level, body mass index (BMI), sunscreen use, outdoor activities, pollution, comorbidities such as malabsorption syndromes and drugs that interfere with vitamin D metabolism such as ant seizure medication or glucocorticoids [11,13,14].

The assessment of accurate levels of vitamin D in critically ill patients is difficult due to acute fluid changes and the inflammatory status, which can alter interpretation of vitamin D. [15] During critical illness, there is an increase in the tissue demand for vitamin D. Altered diastolic blood pressure and albumin levels in the context of inflammation, fluid shifts, capillary leaks, and renal wasting are likely to have a strong influence on the bioavailability of the vitamin D pool [15-18]. Whether vitamin D deficiency affects illness severity and clinical outcomes has been the subject of much debate, with vitamin D deficiency in morbidity and mortality. Despite the increased progress in medical sciences, critically ill patients are still at high risk for mortality and morbidity. Some of these risk factors are modifiable, and their identification and management can improve the outcome.

The purpose of the study was to investigate the correlation of vitamin D deficiency with mortality in critically ill patients. The correlation of vitamin D status and various mortality predictors, such as the APACHE II score at admission to the ICU, the SOFA scores throughout the ICU stay, the number of ventilator days hospital stay and length of stay in the ICU were also analyzed.

MATERIALS AND METHODS

It was a prospective observational study. It was carried out after approval from the institutional ethics committee (IEC / ABSIMS / RMLH / 212) and the Indian clinical trial registry (CTRI / 2021 / 02 / 031248). The inclusion criteria were all patients with stay in the intensive care unit (ICU) stay > 48 hours and willingness to give informed consent. Consent refusal, age less than 18 years, resuscitated patient prior to admission to ICU, pregnant and lactating mothers, patients on multivitamin or nutritional supplements at home, Chronic malabsorption syndrome or chronic diarrhoea. Cancer patients were excluded.

The sample size was calculated using a study by Vipul P et al. [19] The proportion of patients in the ICU with vitamin D deficiency who achieve mortality is 14.77%. Therefore, the minimum sample size for the study using the Cochran formula for the observational study with a confidence level of 95% and a margin of error of 10% was 50. However, we studied all patients admitted to the ICU during the 1 year. The study method included patients being admitted to an intensive care unit and meeting inclusion and exclusion criteria. Blood samples were drawn for vitamin D levels within the first 24 hours after admission to the ICU. Measure 25- hydroxyvitamin D [25(OH)D] levels as a form of vitamin D using electrochemiluminescence methods.

The patients were divided into two groups according to vitamin D, vitamin D Deficiency Group levels <20 ng / ml and Non-Vitamin D Deficiency Group B levels > 20ng/ml. In addition, we studied the correlations of mortality and morbidity in two groups. The following data was collected during the study period. Demographic data like age, sex, weight, comorbidities & admission category. Scores and other clinical details such as APACHE II score (acute physiology and chronic health evaluation) at admission to ICU, SOFA (sequential organ failure assessment) scores for the period of stay in the ICU, ICU morbidities on need for mechanical ventilation, Inotrope use, length of ICU stay. Outcomes in the ICU include discharge or mortality.

The primary objective of this study was to correlate vitamin D with mortality in critically ill patients. Secondary objectives of this study were to correlate deficiency of vitamin D deficiency with morbidity in the ICU such as inotrope use, number of ventilator days' length of ICU and APACHE II score, SOFA scores and hospital stay. Data analysis was performed with SPSS version 25: 0. All continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile ranges) and all categorical variables were expressed as percentages.

After evaluation, qualitative data were analyzed using the Chi square test and quantitative data using Independent t-Test or Mann–Whitney U test to find the relationship between various parameters with vitamin D deficiency. Correlations of vitamin D levels with mortality in the ICU were performed by spearman rho. A multivariate analysis was performed on the entire study population, choosing ICU mortality as the dependent variable and the associated risk factors for ICU mortality were analysed using relative risk (RR). The level of significance was assumed at <5% i.e. P-value<0.05.

RESULTS

A total of 756 patients were evaluated, 594 patients were excluded from the study according to exclusion criteria, and 162 patients included and completed the study. The main reason for exclusion was not being in the ICU for > 48 hours. Demographic data were comparable for the vitamin D deficient group and the non-deficient vitamin D group and there was no significant differences were found in demographic profiles between the two groups, that is, the age, gender, weight and height. Out of 162 patients admitted to the ICU for > 48 hours, the prevalence of vitamin D deficiency in our study was 140 (86.4%) and nondeficient 22 (13.6%) (Table 1).

Table 1. Shows vitamin D deficiency and vitamin D nondeficiency.

Vitamin D	Frequency	Percent(%)
Deficient (< 20 ng/mL)	140	86.4
Non Deficient (≥ 20 ng/mL)	22	13.6

Co-morbidities such as cardiac diseases, respiratory diseases, renal diseases, liver diseases, hypertension, diabetes, and thyroid diseases did not appear to have a significant association with the prevalence of vitamin D deficiency (Table 2). The means of baseline investigations on the day of admission to the ICU such as calcium, phosphorus, urea, creatinine, hemoglobin, and albumin were compared with both groups, but were found to be statistically insignificant. The mean vitamin D levels in the Deficient group and the Non-Deficient group were 10.95 (±5.375) and 14.35 (±6.590) respectively, were statistically significant (p-value <0.03) (Table 3).

The mean duration of stay in ICU was 7.06 (±2.778) days for the vitamin D deficient group and 5.73 (±2.622) days for the non-deficient group. A patient with vitamin D deficiency had a prolonged stay in the ICU and was found to be statistically significant. The mean (SD) SOFA score of patients of the vitamin D deficient group was found to be 3.30 (± 2.855) and the vitamin D non-deficient group was 2.10 (±2.637), so the vitamin D deficient group had statistically significantly higher SOFA scores. We also analysed APACHE II (on admission), number of ventilator days, and hospital stay among two groups that were found to be statistically insignificant as morbidity due to vitamin D deficiency (Table 4).

Table 2. Correlation of vitamin D status with admission diagnosis group patients Co morbidities.

Comorbidity		Vitamin D status		Total	p- Value
		Deficient	Non Deficient		
Cardiac diseases	Present	18	2	20	0.620
	Absent	122	20	142	
Pulmonary diseases	Present	27	6	33	0.390
	Absent	113	16	129	
Renal diseases	Present	18	1	19	0.260
	Absent	122	21	143	
Liver diseases	Present	13	1	14	0.460
	Absent	127	21	148	
Hypertension	Present	35	7	42	0.490
	Absent	105	15	120	
Diabetes	Present	44	7	51	0.970
	Absent	96	15	111	
Thyroid diseases	Present	21	2	23	0.460
	Absent	119	20	139	

Data analysed by Chi-square test. p- Value < 0.05 significant.

Table 3. Correlation of vitamin D status with various investigations.

Variable	Vitamin D	Mean	Std. Deviation	p- Value
Calcium	Deficiency	8.609	.7167	0.611
	Non Deficient	8.691	.5639	
Phosphorus	Deficiency	3.513	.6944	0.430
	Non Deficient	3.391	.5070	
Urea	Deficiency	40.137	29.0698	0.298
	Non Deficient	33.545	13.1357	
Creatinine	Deficiency	1.20	.66	0.098
	Non Deficient	.96	.32	
Hemoglobin	Deficiency	9.925	2.0885	0.491
	Non Deficient	10.259	2.2319	
Albumin	Deficiency	3.014	.4673	0.558
	Non Deficient	3.078	.4786	
Vitamin D levels	Deficiency	10.95	5.375	**0.030**
	Non Deficient	14.35	6.590	

Data analysed by independent t-test. P < 0.05 is significant.

Table 4. Correlation of vitamin D status and various mortality predictors.

	Vitamin D	Mean	Std. Deviation	p- Value
Duration of stay in ICU	Deficiency	7.06	2.778	**0.036**
	Non Deficient	5.73	2.622	
APACHE II (Admission)	Deficiency	9.00	4.431	0.307
	Non Deficient	7.50	4.032	
Number of ventilator days	Deficiency	3.91	2.836	0.408
	Non Deficient	3.36	2.985	
SOFA score	Deficiency	3.30	2.855	0.045
	Non Deficient	2.10	2.637	
Hospital stay	Deficiency	10.51	4.586	0.901
	Non Deficient	10.64	4.054	

Data analysed by independent t-test. P < 0.05 is significant.

In this study, patients in the vitamin D deficient group had a significantly higher mortality rate compared to the patient in the non-deficient group. The mortality rate in the vitamin D deficient group was 40% compared to 18.18% in the non-deficient group. The difference in mortality in both groups for mortality was statistically significant (p-value < 0.05) (Table 5).

Table 5. Correlation of vitamin D status and patient mortality.

Vitamin D	Discharge	Mortality (%)	Total	p Value
Deficient	84 (60%)	56 (40%)	140	0.049
Non Deficient	18 (81.82%)	4 (18.18%)	22	

Data analysed by Chi-square test. p- Value < 0.05 significant.

The mean vitamin D levels were noted to be 10.80 (±4.838) ng/mL in the ICU mortality patient group and 14.78 (±6.201) ng/mL for the ICU discharge patient group. Therefore, patients with a lower vitamin D had higher mortality rates and it was found to be statistically significant (p-Value < 0.05) (Table 6).

Table 6. Correlation of Vitamin D levels and outcome of the ICU (discharge and mortality).

	Outcome	Mean	Std. Deviation	p-Value
Vitamin D levels (ng/mL)	Mortality	10.80	4.838	0.030
	Discharge	14.78	6.201	

Data analysed by independent t-test. P < 0.05 is significant.

Logistic regression analysis was performed to identify factors independently associated with mortality in the ICU. Multivariate analysis with ICU mortality as a dependent variable showed a significant association between risk factors such as – Pulmonary diseases, renal diseases, length of stay in ICU, mechanical ventilation, septic shock, development of MODS (Multiple organ dysfunction syndrome) and SOFA score with ICU mortality (p-Value < 0.05). However, vitamin D deficiency was not associated as an independent risk factor for ICU mortality (p-value 0.320) (Table 7).

Table 7. Logistic regression analysis for the association of independent risk factors with ICU mortality.

Variables	Odds ratio (OR)	95% CI	p-Value
Age	1.007	(0.977 - 1.038)	0.657
Sex	1.029	(0.457 - 2.320)	0.944
Weight	0.996	(0.963 - 1.030)	0.818
Cardiac Diseases	1.146	(0.395 - 3.330)	0.802
Hypertension	1.783	(0.737 - 4.317)	0.200
Diabetes	1.031	(0.448 - 2.374)	0.943
Liver Diseases	2.768	(0.736 - 10.407)	0.132
Thyroid Diseases	2.711	(0.920 - 7.985)	0.070
GCS (on admission)	1.059	(0.862 - 1.301)	0.584
Calcium (on admission)	0.867	(0.485 - 1.549)	0.629
Phosphorus(on admission)	1.622	(0.913 - 2.881)	0.099
Urea (on admission)	1.005	(0.979 - 1.031)	0.710
Creatinine (on admission)	0.566	(0.177 - 1.812)	0.338
Hemoglobin (on admission)	1.234	(1.000 - 1.523)	0.053
Albumin (on admission)	1.190	(0.546 - 2.596)	0.661
Length of ICU stay	5.583	(1.710 - 18.227)	**0.004**
Hospital stay	0.558	(0.152 - 2.055)	0.381
APACHE II (on admission)	0.701	(0.454 - 1.083)	0.109
Vitamin D Levels	1.220	(0.825-1.805)	0.320
Mechanical ventilation	2.124	(1.084- 4.187)	**0.020**
Septic shock	2.297	(1.198- 4.412)	**0.003**
Inotropes use	3.023	(0.010 - 6.599)	0.256
MODS	6.558	(2.789 - 15.420)	**0.001**
SOFA score	3.785	(2.470 – 5.799)	**0.001**

OR, odds ratio, CI – confidence interval. P < 0.05 is significant.

DISCUSSION

Vitamin D is ubiquitous nature, with its functioning in multiple domains of the human body. The question remains: Is vitamin D deficiency a syndrome that is replete, a marker of severe illness, or both? Vitamin D is fat soluble; thus, it enters cells acting as a possible steroid hormone to govern hormonal pathways. The present study aimed to determine whether vitamin D deficiency was associated with mortality after admission to the ICU or increases in ICU morbidities. By doing so, one might be able to predict those at high risk and interventional measures could be planned in advance to improve the outcome after such a complication, achieving a better outcome and a more efficient use of hospital and intensive care resources.

Regarding age, it has been proposed that vitamin D deficiency in the elderly can be attributed to a decrease in the skin's capacity to produce vitamin D due to ageing, because the 7-dehidrocholesterol skin content as well as the response to UV radiation decreases with aging, resulting in a 50% decrease in cutaneous production of pre-vitamin D, from a lack of exposure to sunlight, or from a deficient dietary intake. In addition to the decrease in 25 (OH) D levels, elderly people have a decrease in 1,25-dihydroxyvitamin D renal production due to the generalized decline in renal function associated with aging, a decrease in intestinal calcium absorption, resistance to the action of 1,25 (OH) D in the bowel, and a decrease in the number of cellular receptors of vitamin D (VDR) [20]. In this study, 84.7% of men and 88.3 % of females had vitamin D deficiency. Females had a higher prevalence of vitamin D deficiency, which was statistically insignificant. Vitamin D status being lower in women than in men was reported in some Alharbi et al. [21], Cashman et al. [22], and Souse et al. [23] previous studies. One of the reasons for this gender difference could be the effect of adipose tissue on vitamin D levels. It is well known that the percentage of fat mass is higher in women than that of men. Alternatively, the effect of volumetric dilution could explain the lower vitamin D in people with more adipose tissue. This means that in an individual with a larger fat mass, the fat mass in effect has diluted vitamin D, so less vitamin D is present in the circulation [24].

In this study, mortality in the vitamin D deficient group was 56 (40%) and in the non-deficient group it was 4(18.18%), which was significantly lower in the non-deficient group. A very important observation in this study worth considering was that the mean vitamin D level was significantly higher among discharged patients than among those with mortality as an outcome. Although some studies have reported positive associations with vitamin D deficiency and mortality [4,19,25]. In this study, we found a correlation between mortality and vitamin D deficiency in a univariate analysis; however, vitamin D deficiency was not found as an independent risk factor for mortality in a multivariate analysis. This correlates well with the study by Buchtele et al. [26] but not with Zapatero A et al. [27] Variables showed a significant association –length of stays in the ICU, mechanical ventilation, septic shock, development of MODS and SOFA score were the variables that were independent predictors of mortality.

Mortality among discharged patients for both groups was higher, but the vitamin D deficient group had a higher mortality. It was statistically insignificant. Similar result was found in a study by Yoo et al. which concluded higher mortality among discharged patients [28]. It also evaluated various mortality predictors such as number of ventilator days, hospital stay, and APACHE II (on admission) in both groups. Although most predators had higher mortality in the vitamin D deficient group, the prolonged stay in the ICU in the vitamin D deficient group showed statistical significance. Studies by authors such as Kumar et al. [29], Guan et al. [30] showed vitamin D deficiency associated with prolonged stay in the ICU. In this study, the mean SOFA score in patients of the vitamin D deficient group was found to be 3.30 and the vitamin D non-deficient group was 2.10. The vitamin D deficient group had significantly higher SOFA scores. This correlates well with a recent study by Ji-Hyun Lee et al. who have reported that patients with vitamin D deficiency have higher SOFA scores [31].

The limitations of this study were the small sample size and the short duration of the study period. Participants were recruited from only one tertiary care hospital. The results would be more precise and generalised if the participants were recruited from multiple tertiary care hospitals. Studies with a larger sample size and long duration of the study period are required to produce more robust findings.

CONCLUSIONS

The vitamin D-deficient group had a significantly higher mortality rate compared to the patient in the non-deficient group. But vitamin D deficiency was not found to be an independent risk factor for mortality. Maintaining sufficient vitamin D levels appears to have a potential positive impact on reducing the risk of mortality in critically ill patients admitted to intensive care units, suggesting a beneficial role of adequate vitamin D status in their prevention of mortality.

SUPPLEMENTARY INFORMATION

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REFERENCES

[1] Holick MF. Sunlight, UV Radiation, Vitamin D, and Skin Cancer: How Much Sunlight Do We Need? Adv Exp Med Biol. 2020; 1268: 19-36.
doi: https://doi.org/10.1007/978-3-030-46227-7_2

[2] Jodar E, Campusano C, de Jongh RT, Holick MF. Calcifediol: a review of its pharmacological characteristics and clinical use in correcting vitamin D deficiency. Eur J Nutr. 2023; 62(4): 1579-1597.
doi: https://doi.org/10.1007/s00394-023-03103-1

[3] Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M, Tmava Berisha A, et al.. Vitamin D deficiency 2.0: an update on the current status worldwide. Eur J Clin Nutr. 2020; 74(11): 1498-1513. doi: https://doi.org/10.1038/s41430-020-0558-y

[4] Langlois PL, D'Aragon F, Manzanares W. Vitamin D in the ICU: More sun for critically ill adult patients? Nutrition 2019; 61: 173-178. doi: https://doi.org/10.1016/j.nut.2018.11.001

[5] Atalan HK, Güçyetmez B. Serum Vitamin D Level at ICU Admission and Mortality. Turk J Anaesthesiol Reanim. 2017; 45(4): 193-196. doi: https://doi.org/10.5152/TJAR.2017.60234

[6] Untersmayr E, Kallay E. Insights in Immuno-Nutrition: Vitamin D as a Potent Immunomodulator. Nutrients 2020; 12(11): 3554. doi: https://doi.org/10.3390/nu12113554

[7] Greiller CL, Suri R, Jolliffe DA, Kebadze T, Hirsman AG, Griffiths CJ, et al.. Vitamin D attenuates rhinovirus-induced expression of intercellular adhesion molecule-1 (ICAM-1) and platelet-activating factor receptor (PAFR) in respiratory epithelial cells. J Steroid Biochem Mol Biol. 2019; 187: 152-159. doi: https://doi.org/10.1016/j.jsbmb.2018.11.013

[8] Gao N, Raduka A, Rezaee F. Vitamin D3 protects against respiratory syncytial virus-induced barrier dysfunction in airway epithelial cells via PKA signaling pathway. Eur J Cell Biol. 2023; 102(3): 151336. doi: https://doi.org/10.1016/j.ejcb.2023.151336

[9] Ismailova A, White JH. Vitamin D, infections and immunity. Rev Endocr Metab Disord. 2022; 23(2): 265-277. doi: https://doi.org/10.1007/s11154-021-09679-5

[10] Liu P, Li F, Xu X, Li S, Dong X, Chen L, et al.. 1,25(OH)2D3 provides protection against diabetic kidney disease by downregulating the TLR4-MyD88-NF-κB pathway. Exp Mol Pathol. 2020; 114: 104434. doi: https://doi.org/10.1016/j.yexmp.2020.104434

[11] Pludowski P, Takacs I, Boyanov M, Belaya Z, Diaconu CC, Mokhort T, et al.. Clinical Practice in the Prevention, Diagnosis and Treatment of Vitamin D Deficiency: A Central and Eastern European Expert Consensus Statement. Nutrients 2022; 14(7): 1483. doi: https://doi.org/10.3390/nu14071483

[12] Camacho PM, Petak SM, Binkley N, Clarke BL, Harris ST, Hurley DL, et al.. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis — 2016. Endocr Pract. 2016; 22(Suppl 4): 1-42. doi: https://doi.org/10.4158/EP161435.GL

[13] Bouillon R, Antonio L, Olarte OR. Calcifediol (25OH Vitamin D3) Deficiency: A Risk Factor from Early to Old Age. Nutrients 2022; 14(6): 1168. doi: https://doi.org/10.3390/nu14061168

[14] Van Schoor N, Lips P. Global Overview of Vitamin D Status. Endocrinol Metab Clin North Am. 2017; 46(4): 845-870. doi: https://doi.org/10.1016/j.ecl.2017.07.002

[15] Chang SW, Lee HC. Vitamin D and health - The missing vitamin in humans. Pediatr Neonatol 2019; 60(3): 237-244. doi: https://doi.org/10.1016/j.pedneo.2019.04.007

[16] Amrein K, Hoffmann M, Lobmeyr E, Martucci G. Vitamin D in critical care: where are we now and what is next? Curr Opin Crit Care. 2021; 27(4): 378-384. doi: https://doi.org/10.1097/MCC.0000000000000849

[17] Liu D, Meng X, Tian Q, Cao W, Fan X, Wu L, et al.. Vitamin D and Multiple Health Outcomes: An Umbrella Review of Observational Studies, Randomized Controlled Trials, and Mendelian Randomization Studies. Adv Nutr. 2022; 13(4): 1044-1062. doi: https://doi.org/10.1093/advances/nmab142

[18] Charoenngam N, Holick MF. Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients 2020; 12(7): 2097.
doi: https://doi.org/10.3390/nu12072097

[19] Vipul P, Shuchi C, Avinash A, Manish G, Sukriti K, Ved P. Correlation of Serum Vitamin D Level with Mortality in Patients with Sepsis. Indian J Crit Care Med. 2017; 21(4): 199-204.
doi: https://doi.org/10.4103/ijccm.IJCCM_192_16

[20] De Jongh RT, van Schoor NM, Lips P. Changes in vitamin D endocrinology during aging in adults. Mol Cell Endocrinol. 2017; 453: 144-150.
doi: https://doi.org/10.1016/j.mce.2017.06.005

[21] Alharbi AF, Ali M, Alrefaey YI, Filimban HA, Alhwaity AS, Alamoudi A, et al.. Association Between Serum Vitamin D Levels and Body Mass Index Status: A Cross-Sectional Study at King Khalid Hospital, Jeddah, Saudi Arabia, From 2019 to 2020. Cureus 2023; 15(10): e46927.
doi: https://doi.org/10.7759/cureus.46927

[22] Cashman KD. Vitamin D Deficiency: Defining, Prevalence, Causes, and Strategies of Addressing. Calcif Tissue Int. 2020; 106(1): 14-29.
doi: https://doi.org/10.1007/s00223-019-00559-4

[23] Sousa SES, Sales MC, Araújo JRT, Sena-Evangelista KCM, Lima KC, Pedrosa LFC. High Prevalence of Hypovitaminosis D in Institutionalized Elderly Individuals is Associated with Summer in a Region with High Ultraviolet Radiation Levels. Nutrients 2019; 11(7): 1516.
doi: https://doi.org/10.3390/nu11071516

[24] Karacan M, Usta A, Biçer S, Baktir G, İpek Gündogan G, Sancakli Usta C, Akinci G. Serum vitamin D levels in healthy urban population at reproductive age: effects of age, gender and season. Cent Eur J Public Health. 2020; 28(4): 306-312.
doi: https://doi.org/10.21101/cejph.a5947

[25] Malinverni S, Ochogavia Q, Lecrenier S, Scorpinniti M, Preiser JC, Cotton F, et al.. Severe vitamin D deficiency in patients admitted to the emergency department with severe sepsis is associated with an increased 90-day mortality. Emerg Med J. 2023; 40(1): 36-41.
doi: https://doi.org/10.1136/emermed-2021-211973

[26] Buchtele N, Lobmeyr E, Cserna J, Zauner C, Heinz G, Sengölge G, et al.. Prevalence and Impact of Vitamin D Deficiency in Critically Ill Cancer Patients Admitted to the Intensive Care Unit. Nutrients 2020; 13(1): 22.
doi: https://doi.org/10.3390/nu13010022

[27] Zapatero A, Dot I, Diaz Y, Gracia MP, Pérez-Terán P, Climent C, et al.. Severe vitamin D deficiency upon admission in critically ill patients is related to acute kidney injury and a poor prognosis. Med Intensiva (Engl Ed). 2018; 42(4): 216-224.
doi: https://doi.org/10.1016/j.medin.2017.07.004

[28] Yoo JW, Jung YK, Ju S, Lee SJ, Cho YJ, Jeong YY, et al.. Serum vitamin D binding protein level, but not serum total, bioavailable, free vitamin D, is higher in 30-days survivors than in nonsurvivors with sepsis. Medicine (Baltimore). 2020; 99(25): e20756.
doi: https://doi.org/10.1097/MD.0000000000020756

[29] Kumar D, Singh MV, Yadav RK, Singh DK, Singh DK, Siddiqui SA. Vitamin D levels in paediatric intensive care unit patients and its relation to severity of illness: An Indian experience. Trop Doct. 2021; 51(3): 361-365.
doi: https://doi.org/10.1177/0049475521992999

[30] Guan J, Shichen M, Liang Z, Yu S, Zhao M, Zhang L, et al.. Potential benefits of vitamin D for sepsis prophylaxis in critical ill patients. Front Nutr. 2023; 10: 1073894.
doi: https://doi.org/10.3389/fnut.2023.1073894

[31] Lee JH, Doo SR, Kim D, Park YK, Park EJ, Lee JM. Vitamin D deficiency and mortality among critically ill surgical patients in an urban Korean hospital. Int J Vitam Nutr Res. 2022; 92(2): 101-108.
doi: https://doi.org/10.1024/0300-9831/a000639