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Low levels of vitamin D are associated with nosocomial infections but not with short-term mortality in critically ill patients

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Background/aim: A prospective observational study was conducted to determine the relationship between vitamin D deficiency and nosocomial infections among intensive care unit (ICU) patients.

Materials and methods: Demographic data, season of admission, vitamin D levels at admission, premorbid lifestyle scores, comorbid conditions, and admission diagnosis were recorded in 306 ICU patients. Infections that developed at least 48 h after admission to the ICU were the primary outcome, and ICU, hospital, and 1-year mortality were the secondary outcomes. Infections were evaluated for 28 days, and for the entire duration of ICU stay independently. Multiple logistic regression analysis was performed to control for confounding factors that were statistically significant in univariate analysis.

Results: All infection and mortality rates were significantly higher in low 25 (OH) D groups in univariate analysis. After adjusting for confounding factors, infection rates remained higher in the deficient group. However, ICU and hospital mortality did not show any statistically significant difference between deficient and nondeficient groups. Only the 1-year mortality rate was significantly higher among patients with 25 (OH) D levels less than 20 ng/mL.

Conclusion: Low vitamin D levels are significantly associated with ICU-related infections but not with ICU or hospital mortality. However, further studies are needed to identify the role of vitamin D deficiency in predicting ICU outcomes.

Key words: Vitamin D, nosocomial infections, intensive care

1. Introduction

1.1. Background

Intensive care unit (ICU)-acquired infections are associated with increased mortality, morbidity, and healthcare costs. An overall infection rate of 46%–60% has been reported (1). ICU-acquired infections are associated with a doubling in risk of hospital death (2). The mortality rate has been reported to be as high as 70% (3). Factors such as disease severity, comorbid conditions, indwelling catheterization, and age have been studied as risk factors for infection in ICU patients (4,5).

Recently, vitamin D has been shown to play an essential role in modulating the immune response (6,7). It stimulates the expression of antimicrobial peptides from monocytes, prevents excessive expression of inflammatory cytokines, and amplifies the effect of macrophages (8).

Vitamin D is first metabolized in the liver to its major circulating metabolite, 25-hydroxyvitamin-D (25 (OH) D), and then in the kidneys to its active form, 1,25-$(OH)_2$-D. 25 (OH) D reflects the total amount of vitamin better than other metabolites. It is measured to determine the status of vitamin D. Various definitions of insufficiency and deficiency have been established according to 25 (OH) D levels (9).

In the last decade, studies have been performed to investigate the incidence of 25 (OH) D deficiency and its association with adverse outcomes among critically ill patients (10–17). Most studies have focused mainly on mortality. Growing evidence supports that 25 (OH) D deficiency is independently associated with short- and long-term mortality (18–20). However, the relationship between vitamin D levels and ICU-acquired infections has not been well examined.

Therefore, we aimed to determine whether vitamin D deficiency (assessed by serum 25 (OH) D concentration) is a risk factor for nosocomial infections and mortality among critically ill patients. It was expected that patients with low levels of vitamin D would be more prone to infections and death.

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2. Materials and methods

2.1. Study design and setting

A concurrent observational cohort study was carried out in a 27-bed mixed ICU in a tertiary care hospital (İzmir Tepecik Training and Research Hospital) in İzmir between June 2011 and June 2012. The study was approved by the hospital ethics committee, according to the Declaration of Helsinki. Informed consent was obtained from patients or their family members if patients were not capable of providing consent. During this period, 573 patients were admitted to our ICU. Patients were excluded if they were younger than 18 years old or pregnant; had a malignancy, immune deficiency, or parathyroid dysfunction; or stayed for less than 48 h in the ICU. Patients who survived for 48 h or less were also excluded. If a patient was admitted on more than one occasion, only the first occasion was evaluated. Patients who received vitamin D supplementation were excluded. The association between 25 (OH) D levels with ICU-acquired infections was the primary endpoint, while association with mortality was the secondary endpoint. Covariates were age, sex, season, premorbid lifestyle score (PLS), disease severity score, comorbid conditions, and admission diagnosis. Demographic data (age, sex, and premorbid lifestyle score), simplified acute physiology score (SAPS) II, season of admission, 25 (OH) D levels, PLS score, comorbid conditions, and admission diagnosis were recorded after ICU admission. Blood samples for 25 (OH) D levels were taken at admission along with other routine laboratory tests on the first workday. Serum levels were measured with electrochemiluminescent immunoassays on a Cobas e411 analyzer (Roche Diagnostics) and recorded.

The season of admission was recorded according to astronomical definition: dates between 21 March and 20 June were recorded as spring, between 21 June and 22 September as summer, between 23 September and 20 December as autumn, and between 21 December and 20 March as winter.

PLS was used to describe the patient's performance status prior to acute illness. We classified patients into four groups: unlimited activity, limited activity, homebound, and chair or bed-bound (21).

Comorbid conditions documented in the past medical history were recorded according to ICD-10 coding. ICU-acquired infection was defined as an infection that developed more than 48 h after ICU admission and was diagnosed by an infection specialist who visited the patients every workday. Infections during the first 28 days, and the entire ICU stay, were recorded independently.

ICU, hospital, and 1-year mortality were recorded. If the patient was discharged from the hospital, information about 1-year mortality was obtained from the population registration system.

Because there is no consensus on optimal 25 (OH) D levels among the ICU population, we categorized them into six different groups. The cutoff points were 5, 10, 15, and 20 ng/mL. We did not use higher cutoff levels because there were only 12 patients with 25 (OH) D levels higher than 25 ng/mL.

2.2. Statistical methods

IBM SPSS Statistics version 22.0 (IBM Corp, Somers, NY, USA) was used for statistical analysis. Normality was assessed using the Kolmogorov-Smirnov test. Because all continuous data were nonnormally distributed, they were expressed as the median and interquartile range (IQR) and were compared using the Mann–Whitney U-test. Categorical data were expressed as the number (n) and percentage (%) of events and were compared by Pearson's chi-squared or Fisher's exact test. Data were analyzed at a confidence level of 95%. A P-value less than 0.05 was considered statistically significant.

We used binary logistic regression models to estimate unadjusted and adjusted odd ratios (ORs) of ICU-acquired infections and mortality in different 25 (OH) D groups. ORs were adjusted for age, SAPS II, sex, season, comorbidities, PLS scores, and admission diagnosis. The "purposeful selection of variables" was used for the selection of covariates for logistic regression to create the best model (22).

Multicategory covariates (season, comorbidities, PLS scores, and admission diagnosis) were specified as separate variables to exclude dummy categories. Adjusted residuals in the chi-squared test were used to determine the significance category. Therefore, final covariates with a P-value greater than 0.25 were selected for the pre-model. The variables that were not significant in this multivariate model at the 0.1 alpha level were removed in subsequent steps. If the removing variable changed the estimated OR by more than 20% in the iterative process, it was re-included in the model.

3. Results

During the study period, a total of 306 of 573 patients were enrolled. The main reason for nonparticipation was unavailable 25 (OH) D levels due to technical problems (32% of nonparticipants), while the second most common was death or discharge within 48 h of admission (28%). Malignancy, patient refusal, pregnancy, and known parathyroid dysfunction were other reasons for exclusion.

Baseline characteristics of the subjects are shown in Table 1. The majority of patients were male (60.5%), with a median (IQR) age of 65.00 (52.00–77.00) years and a median (IQR) SAPS II score of 59 (44.75–77.25).

Furthermore, 42%, 65%, 84%, and 91% of patients had 25 (OH) D levels lower than 5, 10, 15, and 20 ng/mL, respectively. The median 25 (OH) D concentration was 6.31.

Table 1. Patients' baseline characteristics and 25 (OH) D levels.

	Median (IQR)		P	Comparison of pairwise	P	Adj. P
Female (121) / Male (185)	4.19 (3.00–8.01) / 8.74(4.04–14.12)		0.000			
Bedridden (29) Homebound (84) Limited activity (61) Unlimited (132)	4.22 (3.00–9.90) 4.21 (3.00–9.88) 5.55 (3.19–11.69) 9.07 (4.19–14.12)		0.001	Homebound-unlimited Bedridden-unlimited	0.000 0.007	0.000 0.043
Trauma (42) Elective surgery (40) Emergency surgery (76) Medical (148)	11.07 (7.26–19.57) 6.32 (3.80–11.50) 4.00 (3.00–7.85) 6.47 (3.62–12.27)		0.000	Trauma-elective surgery Trauma-emerg Surgery Trauma-medical Medical-emerg surgery	0.007 0.000 0.001 0.001	0.042 0.000 0.006 0.004
Spring / summer / autumn / winter	5.79 (3.14–11.19) / 8.60 (4.26–14.62) 5.42 (3.00–11.84) / 4.45 (3.00–9.49)		0.000	Summer-winter Summer-autumn	0.000 0.002	0.000 0.012
Cardiovascular (175) (Y/N)	5.30 (3.00–11.22) / 8.06 (3.76–14.10)		0.013			
Respiratory (106) (Y/N)	5.48 (3.00–11.30) / 6.55 (3.51–12.36)		0.278			
Endocr-metab (122) (Y/N)	4.26 (3.00–9.47) / 8.26 (4.00–13.54)		0.000			
Neurologic (99) (Y/N)	4.80 (3.00–11.61) / 6.90 (3.83–12.27)		0.035			
	<5 (129)	>5 (177)	P	<10 (200)	>10 (106)	P
Age	67.00 (57.00–79.00)	62.00 (46.50–74.50)	0.000	66.00 (55.00–78.00)	63.00 (45.50–74.00)	0.010
SAPS	64.00 (51.00–79.50)	53.00 (38.00–72.50)	0.000	60.00 (47.00–78.00)	53.00 (37.00–77.00)	0.012
Sex (F/M)	74/55	47/130	0.000	97/103	24/82	0.000
Bedridden Homebound Limited activity Unlimited	17 47* 28 37	12 37 33 95*	0.000	22 63* 41 74	7 21 20 58*	0.019
Trauma Elective surgery Emergency surgery Medical	6 17 46* 60	36* 23 30 88	0.000	16 27 62* 95	26* 13 14 53	0.000
Spring / summer / autumn / winter	33 / 35 / 25 / 36*	39 / 82* / 28 / 28	0.004	50 / 65 / 36 / 49*	22 / 52* / 17 / 15	0.027
Cardiac	84	91	0.019	125	50	0.011
Respiratory	50	56	0.224	73	33	0.378
Metabolic	69	53	0.000	93	29	0.001
Neurologic	53	46	0.006	69	30	0.305
	<15 (256)	>15 (50)	P	<20 (279)	>20 (27)	P
Age	65.00 (53.00–77.00)	63.00 (34.50–72.25)	0.026	65.00 (52.00–77.00)	64.00 (37.00–74.00)	0.347
SAPS	59.00 (47.00–77.00)	48.50 (32.00–78.25)	0.033	58.00 (46.00–77.00)	60.00 (32.00–81.00)	0.356
Sex (F/M)	109/147	12/38	0.017	114/165	7/20	0.152
Bedridden Homebound Limited activity Unlimited	25 74 54 103	4 10 7 29*	0.141	26 79 57 117	3 5 4 15	0.495
Trauma Elective surgery Emergency surgery Medical	28 33 71* 124	14* 7 5 24	0.003	33 36 74* 136	9* 4 2 12	0.007
Spring / summer / autumn / winter	61 / 91 / 46 / 58	11 / 26* / 7 / 6	0.129	65 / 101 / 51 / 62	7 / 16*/ 2 / 2	0.051
Cardiac	150	25	0.277	159	16	0.820
Respiratory	86	20	0.418	92	14	0.058
Metabolic	109	13	0.039	114	8	0.307
Neurologic	69	30	0.305	92	7	0.524

*Group with statistical significance

Significantly lower levels were observed in patients who were female, homebound, or admitted in winter and for emergency surgery, or who had additional cardiovascular, endocrine-metabolic, or neurologic diseases. In contrast, patients who were active before admission, trauma patients, and those admitted in summer had higher levels. Similar differences were seen between 25 (OH) D categorical groups. The differences were more significant in the group with a cutoff point of 5 ng/mL, while in the 20 ng/mL group they were less significant (Table 2).

Binary logistic regression results showed that being a trauma patient and being admitted during summer decreased the risk of having low 25 (OH) D levels for all categories. However, being female was a risk factor for having 25 (OH) D levels lower than 5, 10, and 15 ng/mL. Lower SAPS II scores and unlimited PLS were associated with levels higher than 5 ng/mL (Table 3).

The patients spent a median (IQR) of 11 (5.00–27.25) days in the ICU and 21 (11.00–40.25) days in the hospital. Five patients did not receive mechanical ventilation and 82 received it for less than 48 h. A total of 133 (43.5%) patients died during their ICU stay. Four patients died during their hospital stay after ICU discharge. A total of 160 (52.3%) patients died within 1 year.

Sepsis, VAP, and UTI were recorded in 134, 106, and 143 patients, and 88%, 95%, and 75% were seen during the first 28 ICU days, respectively.

The median 25 (OH) D levels were significantly lower in patients with sepsis and VAP during both the 28-day period and the entire ICU period. However, no significant difference was observed between patients with and without UTIs.

Patients who died in the ICU, in the hospital, and over the first year, had significantly lower 25 (OH) D levels (Table 4).

According to chi-squared tests, categorical 25 (OH) D groups at different levels showed significant correlations with infection and mortality rates. The highest odds for all infections were seen with 25 (OH) D levels lower than 20 ng/mL, except for those with sepsis, during entire ICU stay. For all mortality rates (ICU, hospital, and 1-year), levels lower than 15 ng/mL had the highest odds (Table 5).

After adjusting for age, SAPS II, sex, season, comorbidities, PLS scores, and admission diagnosis, the cutoff level of 10 ng/mL was the most statistically significant cutoff value for sepsis during the entire ICU stay. A level of 15 ng/mL was the most significant cutoff for sepsis during the first 28 days and for all UTIs, and 20

Table 2. Binary logistic regression for low 25 (OH) D levels.

	Odds	P	HLS (P)	N-R^2
<5 ng/mL				
Female	3.663	0.000	0.299	0.264
Summer	0.386	0.001		
SAPS II	0.987	0.036		
Trauma	0.352	0.040		
Unlimited	0.550	0.043		
<10				
Female	2.953	0.000	0.425	0.162
Summer	0.482	0.005		
Trauma	0.341	0.003		
<15				
Female	2.054	0.049	0.896	0.091
Summer	0.520	0.040		
Trauma	0.386	0.014		
<20				
Summer	0.407	0.031	0.944	0.088
Trauma	0.281	0.005		

HLS: Hosmer–Lemeshow test
N-R^2: Nagelkerke-R squared

Table 3. Relationship of median 25 (OH) D levels to infections and mortality.

		All				<28 day			
		N	Median (IQR)	P	Spearman Rho	N	Median (IQR)	P	Spearman Rho
Sepsis	Yes No	134 172	5.61 (3.00–9.72) 6.53 (3.46–14.15)	0.006	0.157*	118 188	5.62 (3.00–9.47) 6.53 (3.46–14.19)	0.001	0.185*
VAP	Yes No	106 200	4.87 (3.00–10.12) 6.92 (4.00–13.11)	0.002	0.174*	101 205	4.88 (3.00–10.08) 6.90 (3.79–13.13)	0.004	0.166*
UTI	Yes No	143 163	6.94 (3.32–11.47) 5.66 (3.13–14.13)	0.768	0.017**	108 198	6.85 (3.13–10.16) 6.05 (3.35–14.19)	0.358	0.053**
ICU	Yes No	133 173	5.07 (3.00–10.24) 7.41 (4.00–13.71)					0.003	0.172*
Hospital	Yes No	137 169	4.87 (3.00–10.24) 7.75 (4.00–13.98)					0.001	0.192*
One-year	Yes No	160 146	4.82 (3.00–10.14) 8.15 (4.00–14.22)					0.000	0.227*

*Correlation is significant at the 0.01 level
**Correlation is not significant

Table 4. Relationship of categorical 25 (OH) D levels to number of patients with infections and mortality (chi-squared).

ICU acquired infections	During first 28 days		<5 (129)	>5 (177)	P	Odds	95% CI	<10 (200)	>10 (106)	P	Odds	95% CI
		Sepsis	55	63	0.211	1.345	0.845–2.142	95	23	0.000	3.265	1.905–5.596
		VAP	51	50	0.038	1.661	1.026–2.687	75	26	0.022	1.846	1.090–3.127
		UTI	43	65	0.540	0.862	0.535–1.388	75	33	0.267	1.327	0.804–2.190
			<15 (256)	>15 (50)	P	Odds	95% CI	<20 (279)	>20 (27)	P	Odds	95% CI
		Sepsis	113	5	0.000	7.112	2.733–18.506	117	1	0.000	18.778	2.512–140.342
		VAP	91	10	0.032	2.206	1.054–4.618	98	3	0.011	4.331	1.272–14.747
		UTI	101	7	0.001	4.003	1.733–9.246	106	2	0.001	7.659	1.778–32.991
	During entire ICU stay		<5 (129)	>5 (177)	P	Odds	95% CI	<10 (200)	>10 (106)	P	Odds	95% CI
		Sepsis	62	72	0.199	1.350	0.854–2.132	104	30	0.000	2.744	1.655–4.550
		VAP	54	52	0.023	1.731	1.075–2.787	78	28	0.028	1.781	1.062–2.986
		UTI	55	88	0.220	0.752	0.476–1.187	92	51	0.724	0.919	0.573–1.472
			<15(256)	>15 (50)	P	Odds	95% CI	<20 (279)	>20 (27)	P	Odds	95% CI
		Sepsis	124	10	0.000	3.758	1.802–7.837	128	6	0.018	2.967	1.162–7.575
		VAP	95	11	0.040	2.092	1.023–4.279	102	4	0.023	3.314	1.115–9.849
		UTI	128	15	0.010	2.333	1.215–4.481	136	7	0.023	2.717	1.113–6.631
Mortality				<5 (129)	>5 (177)	P	Odds	95% CI	<10 (200)	>10 (106)	P	Odds
		ICU	66	67	0.020	1.720	1.086–2.724	96	37	0.028	1.721	1.059–2.799
		Hospital	69	68	0.009	1.843	1.164–2.920	99	38	0.022	1.754	1.081–2.847
		One-year	82	78	0.001	2.214	1.390–3.527	117	43	0.003	2.065	1.279–3.334
			<15 (256)	>15 (50)	P	Odds	95% CI	<20 (279)	>20 (27)	P	Odds	95% CI
		ICU	119	14	0.016	2.234	1.149–4.341	123	10	0.480	1.340	0.593–3.031
		Hospital	123	14	0.009	2.378	1.224–4.621	127	10	0.397	1.420	0.628–3.212
		One-year	144	16	0.002	2.732	1.436–5.199	150	10	0.097	1.977	0.874–4.469

ng/mL was the most significant cutoff level for all VAPs (Table 5).

The adjusted ORs for ICU and hospital mortality did not show any significant association with low and high 25 (OH) D levels. Only the 1-year mortality rate was found to be higher in patients with 25 (OH) D deficiency. Among the categories, the OR was highest for the cutoff level of 15 ng/mL (Table 5).

Table 5. Unadjusted and adjusted association of 25 (OH) D levels with ICU-acquired infections and mortality.

25 (OH) D		HLS (P)	N-R^2		OR	95% CI	P		HLS (P)	N-R^2	OR	95% CI	P
Sepsis	<5	0.822	0.024	UA	1.345	0.845–2.142	0.212	Whole ICU stay	0.888	0.079	1.350	0.854–2.132	0.199
				A	1.351	0.846–2.158	0.207				1.181	0.732–1.904	0.495
	<10	0.858	0.105	UA	3.265	1.905–5.596	0.000		0.296	0.133	2.744	1.655–4.550	0.000
				A	3.342	1.942–5.749	0.000				2.629	1.563–4.420	0.000
	<15	0.878	0.119	UA	7.112	2.733–18.506	0.000		0.173	0.127	3.758	1.802–7.837	0.000
				A	7.179	2.752–18.724	0.000				3.513	1.660–7.435	0.001
	<20	0.975	0.101	UA	18.778	2.512–140.342	0.004		0.451	0.099	2.967	1.162–7.575	0.023
				A	18.886	2.523–141.391	0.004				2.894	1.109–7.554	0.030
VAPFirst 28 days	<5	0.960	0.112	UA	1.661	1.026–2.687	0.039		0.914	0.128	1.606	1.002–2.573	0.029
				A	1.455	0.879–2.409	0.145				1.509	0.914–2.492	0.107
	<10	0.175	0.119	UA	1.846	1.090–3.127	0.023		0.308	0.132	1.781	1.062–2.986	0.029
				A	1.715	0.993–2.962	0.053				1.579	0.916–2.721	0.070
	<15	0.879	0.117	UA	2.206	1.054–4.618	0.036		0.973	0.143	2.092	1.023–4.279	0.043
				A	1.983	0.926–4.246	0.078				1.810	0.856–3.830	0.121
	<20	0.907	0.133	UA	4.331	1.272–14.747	0.019		0.878	0.140	3.314	1.115–9.849	0.028
				A	4.313	1.237–15.037	0.022				3.101	1.003–9.581	0.037
UTI	<5	0.247	0.085	UA	0.862	0.535–1.388	0.540		0.963	0.115	0.752	0.476–1.187	0.221
				A	0.846	0.508–1.409	0.520				0.642	0.390–1.055	0.080
	<10	0.512	0.090	UA	1.327	0.804–2.190	0.268		0.779	0.104	0.919	0.573–1.472	0.724
				A	1.402	0.823–2.387	0.214				1.179	0.710–1.955	0.525
	<15	0.877	0.143	UA	4.003	1.733–9.246	0.001		0.804	0.128	2.333	1.215–4.481	0.011
				A	4.501	1.890–10.717	0.001				2.383	1.196–4.744	0.013
	<20	0.646	0.145	UA	7.659	1.778–32.993	0.006		0.203	0.128	2.717	1.113–6.631	0.028
				A	9.635	2.175–42.676	0.003				3.122	1.225–7.959	0.017
Mortality													
ICU mortality	<5	0.673	0.287	UA	1.720	1.086–2.724	0.021						
				A	1.041	0.610–1.776	0.884						
	<10	0.816	0.289	UA	1.721	1.059–2.799	0.029						
				A	1.256	0.720–2.192	0.422						
	<15	0.610	0.293	UA	2.234	1.149–4.341	0.018						
				A	1.644	0.772–3.498	0.197						
	<20	0.702	0.281	UA	1.340	0.593–3.031	0.482						
				A	1.279	0.502–3.260	0.607						
Hospital mortality	<5	0.318	0.307	UA	1.843	1.164–2.920	0.009						
				A	1.174	0.685–2.010	0.560						
	<10	0.610	0.309	UA	1.754	1.081–2.847	0.023						
				A	1.310	0.748–2.296	0.345						
	<15	0.723	0.335	UA	2.378	1.224–4.621	0.011						
				A	1.784	0.823–3.867	0.143						
	<20	0.489	0.308	UA	1.420	0.628–3.212	0.399						
				A	1.360	0.526–3.515	0.526						
One-year mortality	<5	0.295	0.382	UA	2.214	1.390–3.527	0.001						
				A	1.595	0.922–2.759	0.095						
	<10	0.263	0.386	UA	2.065	1.279–3.334	0.003						
				A	1.802	1.014–3.201	0.045						
	<15			UA	2.732	1.436–5.199	0.002						
				A	2.531	1.170–5.477	0.018						
	<20			UA	1.977	0.874–4.469	0.102						
				A	1.889	0.705–5.065	0.206						

UA: Unadjusted; A: Adjusted

4. Discussion

In the present study, we hypothesized that low levels of 25 (OH) D would be associated with ICU-acquired infections and mortality. Our data showed that the highest odds were seen with levels lower than 20 ng/mL for infections and lower than 15 ng/mL for mortality in univariate analysis. After adjustment for multiple potential confounders, low levels of 25 (OH) D remained significant predictors for infections and 1-year mortality, but not for ICU and hospital mortality.

Since the number of patients with 25 (OH) D level higher than 25 ng/mL was limited, we did not compare groups with higher cutoff levels.

Bedridden patients had slightly higher 25 (OH) D levels than homebound patients, and compared with patients with unlimited activity, the adjusted P-value was more significant with homebound than bedridden patients. This could be due to the fact that some bedridden patients received enteral nutritional supplements. Because we did not know whether the patient received nutritional supplements, it is impossible to account for this difference. Not querying about it may be a potential source of bias.

We observed a higher incidence of 25 (OH) D deficiency in critically ill patients than previously reported (10–17,23–25). However, most of these studies were from developed countries. Studies from developing countries,

including Turkey, reported lower levels of 25 (OH) D, but were not specific to ICU patients. Identified risk factors were extremes of age, female sex, winter season, dark skin pigmentation, malnutrition, lack of sun exposure, a covered clothing style, and obesity (26,27). The prevalence of hypovitaminosis lower than 5 ng/mL was reported to be as high as 25% in China and Mongolia.

In our cohort, all ICU-related infections and 1-year mortality were associated with low 25 (OH) D levels after adjustment. Among ICU-acquired infections, the most frequently investigated one is sepsis. Jeng et al. showed that 25 (OH) D, vitamin D binding protein (DBP), and cathelicidin (an endogenous antimicrobial peptide) levels were significantly lower in critically ill patients compared to healthy controls, and there was a significant positive association between circulating 25 (OH) D and cathelicidin levels. In a retrospective cohort study with 2399 patients, 25 (OH) D levels lower than 15 ng/mL were associated with blood culture positivity. Cutoff values of 20 and 30 ng/mL were also studied in various cohorts and found to be significantly associated with sepsis (17–23,28–33).

However, there are conflicting results concerning the association of low 25 (OH) D levels with other nosocomial infections. Some researchers could not find any correlation between nosocomial infections and 25 (OH) D levels, while others observed that low levels of vitamin D were associated with a trend toward increased risk of ICU-acquired infections. However, only a few of these relationships were statistically significant (14,28,34). Mixed results were also reported for mortality rates (4,17,27,35).

Our results suggest that patients with low vitamin D levels are prone to ICU-related infections, but low vitamin D may be unrelated to mortality rates.

More studies are needed to evaluate the role of vitamin D in ICU-related infections and mortality. Whether replacement therapy leads to better outcomes in the deficient group also needs to be investigated.

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