Original Article

Prevalence and association of Vitamin D Deficiency and Mortality in patients with Severe Sepsis

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ABSTRACT

Objectives : To determine the prevalence of vitamin D deficiency in severely septic patients and its clinical outcomes, including mortality rate.

Methods : A prospective cross sectional study was conducted to investigate the prevalence of vitamin D deficiency and its association with 30-day mortality in patients with severe sepsis. Patients with severe sepsis admitted to Medicine and ICU wards at tertiary care centre, between Nov. 2017 and Nov. 2019 were included. A 25-hydroxyvitamin D level < 20 ng/mL was defined as vitamin D deficiency. For an association analysis, the patients were grouped into deficient versus not deficient.

Results :75 patients with severe sepsis were enrolled. A total of 57 patients (76%) had vitamin D deficiency and 18 (24%) had no vitamin D deficiency. There was significant association of vitamin D deficiency with female gender (p=0.018), serum calcium levels (p=0.0107), respiratory system involvement (p=0.044), duration of hospital stay (p=0.0227), endotracheal intubation rate (p=0.029), duration of mechanical ventilation (p=0.0269), APACHE II score (p=0.032) and 30-day mortality (p= 0.008), The odds ratio of the 30-day mortality rate was 1.41 (95% confidence interval [CI], 1.05-1.88, p=0.020) for APACHE II score and 38.10 (95% CI, 4.10362.21, p=0.001) for endotracheal intubation.

Conclusion : The prevalence of vitamin D deficiency was very high (76%) among patients with severe sepsis. A significant higher mortality rate, duration of hospital stay, APACHE II score, endotracheal intubation rate and duration of mechanical ventilation was observed, particularly in patients with vitamin D deficiency.

Introduction :

Vitamin D is a steroid prohormone. Its main function is to regulate calcium and phosphate metabolism, and bone homeostasis. however, it is also involved in other physiological functions such as anti-inflammation[1], antiproliferation[1], cellular immune response to infection[2] and cellular gene transcription[3]. Also, it is protective against several chronic illnesses, including the risk of systemic infection, cardiovascular disease, lung disease and diabetes[4].

Vitamin D can suppress inflammatory cytokines (such as interleukin-6 and C-reactive protein)[5], augment anti-inflammatory mediators (such as interleukin-10),[5] and act as an antibacterial peptide (such as cathelicidin).[6,7] Vitamin D deficiency, usually represented as a low serum concentration of 25-hydroxyvitamin D (25(OH)D), has been found to be associated with an increased risk of morbidities, such as acute kidney injury,[8] myocardial infarction,[9] etc. It also correlated with a longer stay in the intensive care unit and higher mortality rate.[10,11,12,13]

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Objectives :

1) To study the prevalence of vitamin D deficiency in patients of severe sepsis admitted in the tertiary care hospital.
2) To study the association between vitamin D deficiency and clinical outcome including mortality in patients of severe sepsis

Materials and Methods :

The study was conducted at tertiary care centre during period Nov. 2017 to Nov. 2019 after taking clearance from institutional ethics committee. patients admitted in medicine wards and ICU were selected. The study design was a prospective observational study. Total 200 patients of suspected sepsis were screened and 75 patients of severe sepsis were selected.

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[14] Severe sepsis is defined as sepsis with organ dysfunction.[15,16] The use of the Sepsis-related Organ Failure (SOFA) score was recommended for defining organ dysfunction during sepsis. According to endocrine society guidelines, serum vitamin 25 (OH) D levels : normal : 30 > ng/ml, insufficient : 20-29.99 ng/ml, deficient : < 20 ng/ml.[17,18]

Exclusion Criteria :

End-stage kidney disease, advanced stage cancer, age more than 65 years, pregnancy, history of glucocorticoids use and vitamin D supplementation.

After a thorough physical examination, routine laboratory investigations including complete blood count (CBC), blood chemistry, serum electrolytes, two-specimen blood-culture, site specific culture as indicated, serum 25 (OH) D levels and chest X-ray were performed. Patients who met the inclusion criteria were assessed to evaluate the severity of illnesses by the Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score at the same time. The serum assay of 25 (OH) D was studied by the fully automated Chemiluminescence immunoassay in fasting sample.

Clinical data collected were age, sex, comorbidities, GCS score APACHE-II score, primary source of infection, endotracheal intubation rate, and duration of mechanical ventilation, length of hospital stay, and 30-day hospital mortality. Patients who were alive were censored after 30 days of follow-up. Laboratory data collected, aside from levels of 25(OH)D, were CBC, blood sugar, blood urea, serum creatinine, serum electrolytes, lactate, total protein, calcium, and phosphate.

Vitamin D status is determined by serum 25 (OH) D level and defined according to the Endocrine Society guidelines : Normal : > 30 ng/ml,i nsufficient : 20-29.9 ng/ml, deficient : < 20 ng/ml. For statistical comparison, we categorized the patients into two groups by their vitamin D level : not deficient (normal and insufficient) versus deficient.

Statistical Analysis : Collected data were entered into Microsoft Excel spreadsheet. Tables and charts were prepared with the help of Microsoft windows 10 Word and excel. Continuous variables were presented as Mean SD. Categorical variables were expressed in frequency and percentages. Continuous variables were compared between vitamin D-deficiency and no vitamin D-deficiency and also between Non-survivors and Survivors by performing an independent t-test for normalized data and for non-normalized data, Mann-Whitney test was used. Categorical variables were compared between cases and control by performing the chi-square test. For a small number, The Fisher exact test was used wherever applicable. Univariate analysis was performed to determine risk factors for mortality in patients of sepsis by calculating Odds ratio, 95% Confidence interval. Multiple regression analysis was performed to determine independent predictors for mortality in patients of sepsis. $P<0.05$ was considered as statistical significance. Statistical software STATA version 14.0 was used for data analysis.

Observations and Results :

Total 75 patients of severe sepsis were included and were evaluated for vitamin D deficiency. ***Table 1*** shows : 57 (76%) patients were vitamin D deficient, 12 (16%) were vitamin D insufficient and 6 (8%) with normal vitamin D levels.

Baseline Characteristics :

The mean age of the study population was 41.56 ± 13.87 years. Out of total 75 patients,36(48%) were males and 39 (52%) were females.The mean age of males was 41.19 ± 13.64 years and of females was 41.89 ± 14.24 years. The maximum number of patients were in the age group of 21-30 years (n=19). There was no significant association between age and vitamin D deficiency (p=0.917). Out of 36 male patients, 23 (63.89%) were vitamin D deficient and 13 (36.11%) were not having vitamin D deficiency. Out of 39 females, 34 (87.18%) were vitamin D deficient. On statistical analysis, the female gender is significantly associated with vitamin D deficiency in patients with severe sepsis (p=0.018).

Correlation of laboratory data including CBC, blood chemistry, ABG, calcium and phosphate levels, and vitamin D deficiency has been shown in ***Table 2.*** We found a statistically significant association between serum calcium level and vitamin D deficiency (p=0.0107). Among various systems involved in severe sepsis, the respiratory system was predominantly involved (n=32). After statistical analysis, the involvement of respiratory system (p=0.044) and urinary system (p=0.032) in patients with severe sepsis was found to be significant in those patients who were having vitamin D deficiency.

Out of 75 patients of severe sepsis, only 6 patients were having APACHE II score = 25, rest 69 patients were having < 25. Out of 6 patients with APACHE II score ≥ 25, all 6 (100%) were vitamin D deficient. Out of 69 patients with APACHE II score < 25, 51 (73.91%) were vitamin D deficient and 18 (26.09%) were not vitamin D deficient. Mean APACHE II score of vitamin D deficient patients was 18.42 ± 5.06 and of not vitamin D deficient patients was 14.72 ± 2.19. The minimum APACHE II score in vitamin D deficient patients was 8 and the maximum was 31. The minimum APACHE II score in no vitamin D deficient patients was 11 and the maximum was 19. On statistical analysis, there was a significant association between the APACHE II score and vitamin D deficiency in patients of severe sepsis (p=0.037).

Vitamin D deficiency and clinical outcome in severe sepsis :

Table 4 shows mean duration of hospital stay in vitamin D deficient patients was 8.73 ± 3.37 SD days, whereas that in patients with no vitamin D deficiency was 6.83 ± 1.33 SD days. Minimum duration of stay in patients with vitamin D deficiency was 6 days and maximum was 25 days, whereas minimum duration of stay in patients with no vitamin D deficient levels was 4 days and the maximum was 9 days. After a statistical analysis association between duration of hospital stay and vitamin D deficiency was found to be significant (p=0.0227).

Table 5 shows out of 75 patients of severe sepsis, 24 patients required endotracheal intubation and 51 patients didn't require endotracheal intubation. Out of 24 intubated patients, 22 (91.67%) were vitamin D deficient and 2 (8.33%) were non-vitamin D deficient patients. Out of 51 non-intubated, 35 (68.62%) were vitamin D deficient and 16 (31.68%) were not having vitamin D deficiency. After statistical analysis, there was a significant association found between endotracheal intubation and vitamin D deficiency (p=0.029).

Table 6 shows mean duration of mechanical ventilation in vitamin D deficient patients was 8.95 ± 3.16 SD days, whereas in patients with no vitamin D deficiency was 3.5 ± 0.70 SD days. The minimum duration of mechanical ventilation in patients with vitamin D deficiency was 4 days and maximum was 15 days, whereas minimum duration of mechanical ventilation in patients with insufficient or normal vitamin D levels was 3 days and the maximum was 4 days. After statistical analysis, there was a significant association between the duration of mechanical ventilation and vitamin D deficiency in patients of severe sepsis (p=0.0269).

Table 7 shows out of 75 patients of severe sepsis, 16 patients expired and the remaining 59 survived. Out of 16 expired patients, all 16 were vitamin D deficient and none was non-vitamin D deficient. Out of 59 survived patients, 41 were vitamin D deficient and 18 were not vitamin D deficient. On statistical analysis, there was a significant association found between 30day-mortality and vitamin D deficiency (p=0.008).

Table 1 : **Serum 25 (OH) D levels in the study population**

Serum 25 (OH) D levels	Frequency	Percentage
Deficient	57	76%
Insufficient	12	16%
Normal	6	8%

Table 2 : **Characteristics of septic patients according to vitamin D deficient and not vitamin D deficient status**

Baseline Characteristics	Vitamin D deficient (<20ng/ml) (n=57)	Not vitamin D deficient (≥ 20 ng/ml) (n=18)	p-value
Age (years)	41 ± 13.529	41.737 ± 15.3047	0.917
Females (%)	34 (59.65%)	5 (27.78%)	0.018
Primary system involved			
1.CNS	2 (3.51)	0	1
2.Constitutional	7 (12.28)	4 (22.22)	0.299
3.GIT	10 (17.54)	4 (22.22)	0.657
4.RS	28 (49.12)	4 (22.22)	0.044
5.HBS	11 (19.30)	1 (5.56)	0.273
6.US	4 (7.02)	5 (27.78)	0.032
Investigations			
Rectal temperature	39.04 ± 1.17	39.0 ± 1.0	0.8735
Heart rate	124 ± 9.85	120.83 ± 9.10	0.2305
SBP	92.63 ± 23.64	95.55 ± 18.85	0.6340
DBP	54.36 ± 18.74	57.22 ± 17.75	0.5704
MAP	67.23 ± 19.16	69.97 ± 17.57	0.5908
RR	29.22 ± 8.03	28 ± 6.99	0.5623
HB	10.71 ± 2.54	11.01 ± 2.63	0.6754
WBC count	23391.58 (12600-184000)	20345 (14010-475000)	0.4871
Platelets	201475.4 (51000-510000)	259166 (72000-475000)	0.1742
Hct	33.01 ± 9.13	32.42 ± 7.0	0.8005
Urea	54.44 ± 42.33	6.55 ± 49.32	0.8232
Creatinine	1.67 ± 2.42	1.26 ± 0.57	0.7229
Sodium	140.71 ± 8.68	136.55 ± 9.0	0.0830
Potassium	3.87 ± 0.72	3.88 ± 0.70	0.9773
Total billirubin	2.72 ± 4.47	1.24 ± 1.10	0.1739
Total protein	5.95 ± 0.69	6.17 ± 0.58	0.2434
PaO2	103.42 ± 47.46	86.36 ± 28.82	0.1542
iO2	21.53 ± 3.81	20.62 ± 0.32	0.3149
PH	7.35 ± 0.09	7.35 ± 0.06	0.9589
PaO2/FiO2	481.71 ± 236.72	408.84 ± 163.81	0.9653
Calcium	8.23 ± 0.21	30.48 ± 9.27	0.0107
Phosphate	3.17 ± 0.44	3.21 ± 0.35	0.7357
Vitamin 25(OH)D	11.20 ± 5.09	30.48 ± 9.27	<0.0001
APACHE II score			0.0037
≥ 25	6	0	
< 25	51	18	

Table 3 : **Correlation of Gender and vitamin D deficiency**

Vitamin D status	Male		Female	
	Frequency	Percentage	Frequency	Percentage
Deficient	23	63.89	34	87.18
Not deficient	13	36.11	5	12.82
P-value	0.018,S			

Table 4 : **Association of duration of hospital stay and vitamin D deficiency**

Duration of hospital stay	Vitamin D deficiency		No vitamin D deficiency		P-value
	Frequency	Percentage	Frequency	Percentage	
5 - 9	41	54.67	18	24	0.0227,S
10 14	14	18.67	0	-	
≥15	2	2.67	0	-	
Mean and range	8.73±3.37, (6-25)		6.83±1.33, (4-9)		

Table 5 : **Association of endotracheal intubation and vitamin D deficiency**

Endotracheal Intubation required or not	Vitamin D deficiency		No vitamin D deficiency		P-value
	Frequency	Percentage	Frequency	Percentage	
Yes	22	91.67	2	8.33	0.029,S
No	35	68.62	16	31.38	

Table 6 : **Association of duration of mechanical ventilation and vitamin D deficiency**

Duration of mechanical ventilation	Patients with vitamin D deficiency		Patients with no vitamin D deficiency	
	Frequency	Percentage	Frequency	Percentage
<5	1	33.33	2	66.67
5 - 10	14	100	0	-
11 - 15	6	100	0	-
>15	0		0	
Mean	8.95 ± 3.16 8 (4 - 15)*		3.5 ± 0.70 3.5 (3 - 4)*	
P-value	0.0269,S			

*Median (Range)

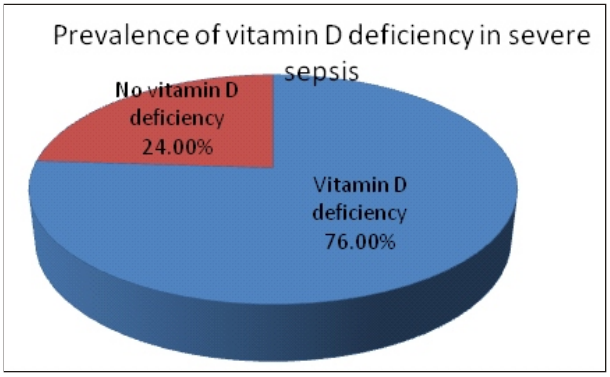
Table 7 : **Association of 30-day mortality and vitamin D deficiency**

Mortality	Patients with vitamin D deficiency		Patients without vitamin D deficiency		P-value
	Frequency	Percentage	Frequency	Percentage	
Yes	16	100	0	-	0.008, HS
No	41	69.49	18	30.51	

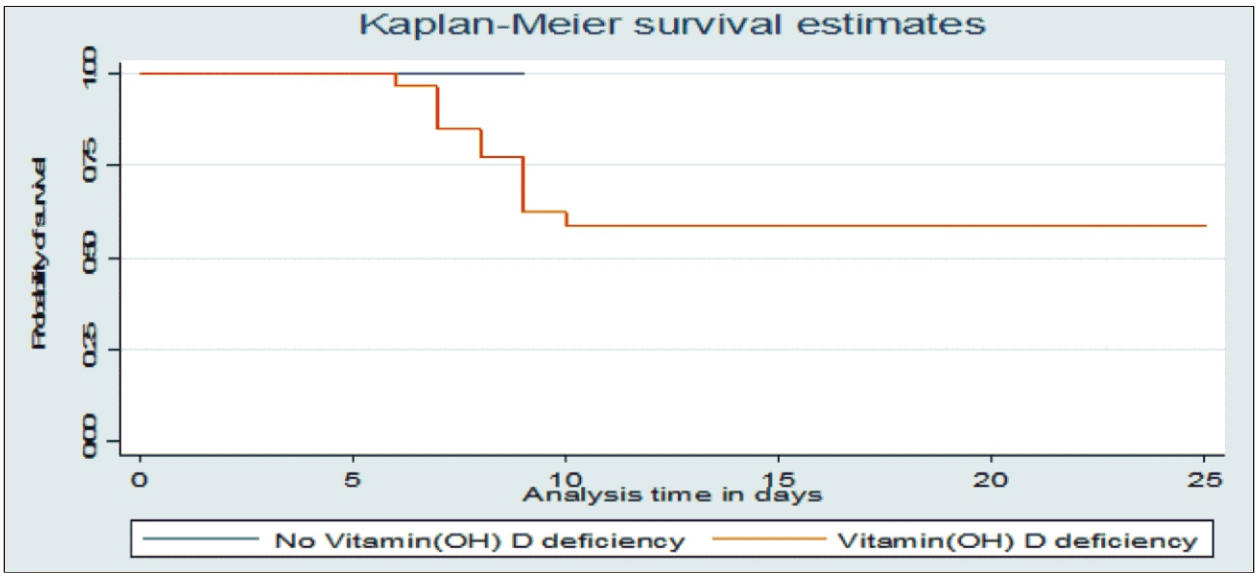
Table 8 : **Multiple logistic regression analysis for predicting risk factors of mortality in patients of severe sepsis**

Risk factor	OR	95% confidence interval	P value
APACHE-II Score	1.41	1.05 1.88	0.020, S
Intubation	38.57	4.10 362.21	0.001, HS

Table 8 shows when the association of various risk factors was studied with 30-day mortality in patients of severe sepsis by multiple logistic regression analysis, APACHE II score (OR = 1.41, QRI 1.05-1.88, p = 0.020) and endotracheal intubation (OR = 38.57, QRI 4.10-362.2, p = 0.001) were found to be independent risk factors for mortality in patients of severe sepsis with vitamin D deficiency.



Graph 1 : **Prevalence of vitamin D deficiency in severe sepsis**



Graph 2 : **Kaplan Meier curve for overall survival in patients with severe sepsis having vitamin 25 (OH) D deficiency**

Graph 2 is Kaplan Meier curve for overall survival in patients with severe sepsis having vitamin D deficiency showing worse survival in patients with vitamin 25 (OH) D deficiency.

Discussion :

Age distribution :

In this study, the mean age of patients was 41.56 ± 13.87 years; with the mean age of males was 41.19 ±13.64 years and of females was 41.89 ± 14.24 years. There was no statistical association between age and vitamin D deficiency.

Sex distribution :

Out of the total of 75 patients of severe sepsis, there were 36 (48%) males and 39 (52%) females. A maximum number of males,10 (27.75%) were in the age group of 41-50 years and maximum females,12 (30.77%) were seen in the age group of 21-30 years of age. There was significant association between

female gender and vitamin D deficiency (p=0.018). This was comparable to studies done by **Trongtrakul K, Feemuchang C**[18] study there were 44% males and 56% were females This reflects the female population was more prone to severe sepsis.

Prevalence of vitamin D in the study population :

Despite the presence of abundant sunlight exposure, vitamin D deficiency in India is as high as 70%100% of ostensibly healthy individuals.[19] In our study, out of a total of 75 cases of severe sepsis, there were about 57 (76%) cases of vitamin D deficiency,12 (16%) cases of vitamin D insufficiency and 6 (8%) cases of normal vitamin D levels. As serum 25 (OH) D is the best predictor of vitamin D levels in serum, it is used in our study. Vitamin D deficiency was most prevalent (76%) in the study population. The distribution was comparable to study carried by **Trongtrakul K, Feemuchang C *et al***[18] who had the majority of the patients of vitamin D deficiency around 75.45% (n=83), vitamin D insufficiency was seen in 15.45% (n=17) and 9.09% (n=10) had normal vitamin D levels. Whereas study carried out by **Karin Amrein, Paul Zajic, Christian Schnedl *et al***[20] shows the majority of all patients were vitamin D deficient (60.2%) or insufficient (26.3%), while normal 25(OH) D levels were present in only 13.6% of the population

Primary system involved :

Out of various systems involved in patients of severe sepsis, statistical analysis shows that vitamin D deficiency was significantly associated with the respiratory system (p=0.044) and urinary system (p=0.032).

Vitamin D has since been studied in several clinical trials to characterize its role in respiratory infections. **Ginde *et al.*** found an inverse relationship between serum 25 (OH) D concentrations and the incidence of upper respiratory infections.[21] This suggests that respiratory system infection is significantly associated with vitamin D deficiency in severe sepsis.

Duration of hospital stay :

Mean of the duration of hospital stay in vitamin D deficient patients was 8.73 ± 3.37 SD, whereas the mean duration of hospital stay in patients with no vitamin D deficiency was 6.83 ± 1.33 SD. Minimum duration of stay in a patient with vitamin D deficiency is 6 days and the maximum duration is 25 days, whereas minimum duration of stay in patients with no vitamin D deficient levels is 4 days and the maximum duration is 9 days. After statistical analysis, vitamin D deficiency was found to be significantly associated with the duration of hospital stay in patients of severe sepsis (p value = 0.0227). **Megan A Rech, Todd Hunsaker *et al***[22] also found a significant association between ICU length of stay and vitamin D deficiency (p=0.02).

Endotracheal intubation :

Out of 24 intubated patients, 22 (91.67%) were vitamin D deficient and 2 (8.33%) were non-vitamin D deficient patients. Out of 51 non-intubated, 35 (68.62%) were vitamin D deficient and 16 (31.68%) were not having vitamin D deficiency. The statistical analysis has shown that vitamin D deficiency significantly increases (p-value 0.029) endotracheal intubation rate in patients of severe sepsis. However, endotracheal intubation is an independent risk factor for the 30-day mortality in patients of vitamin D deficiency (odd's ratio=38.57, CI 4.10 - 362.21). A study by **Moromizato T1, Litonjua AA, Braun AB *et al***[10] shown no association between the rate of endotracheal intubation and vitamin D deficiency.

Duration of mechanical ventilation :

Mean duration of mechanical ventilation in patients of vitamin D deficiency was 8.95 ± 3.16 days and in patients with no vitamin D deficiency was 3.5 ± 0.70 days. Minimum duration of mechanical ventilation in a patient with vitamin D deficiency was 4 days and the maximum duration is 15 days, whereas minimum duration of mechanical ventilation in patients with no vitamin D deficiency was 3 days and the maximum duration was 4 days. Statistical analysis had shown vitamin D deficiency significantly increases (p-value = 0.0269) duration of mechanical ventilation in patients of severe

sepsis. Studies by **Sindhaghatta Venkatram, Sridhar Chilimuri *et al*[12]** and **Moromizato T1, Litonjua AA, Braun AB *et al*[10]** showed that there was no significant association between duration of mechanical ventilation and vitamin D deficiency in patients of severe sepsis.

APACHE II score :

Out of 6 patients with APACHE II score = 25, all 6 (100%) were vitamin D deficient. Out of 69 patients with APACHE II score < 25, 51 (73.91%) were vitamin D deficient and 18 (26.09%) were not vitamin D deficient. Mean APACHE II score of vitamin D deficient patient was 18.42 ± 5.06 and of not vitamin D deficient patient was 14.72 ± 2.19. The Statistical analysis shown that vitamin D deficiency significantly associated with increased APACHE II score in patients with severe sepsis (p=0.037). **Koorosh Ahmadi, Morteza Talebi Doluee *et al*[23]** found a significant inverse association between APACHE II score and vitamin D deficiency in patients of sepsis.

Outcome of severe vitamin D deficiency in severe sepsis :

In this study, out of 16 expired patients, all 16 were vitamin D deficient and none was non-vitamin D deficient. Out of 59 survived patients, 41 (69.49%) were vitamin D deficient and 18 (30.51%) were not vitamin D deficient. After statistical analysis, the p-value was found to be 0.008; which suggested that vitamin D deficiency significantly increases mortality in patients of severe sepsis. The outcome was similar to the study carried out by **Trongtrakul K, Feemuchang C *et al*[18]** in which t patients with severe vitamin D deficiency had a significantly higher percentage of 30-day hospital mortality (23%) vs 4% in non-severe vitamin D deficient patients (p-value = 0.003).

The study by **Sindhaghatta Venkatram, Sridhar Chilimuri *et al*[12]** revealed that the observed mortality was higher than the predicted mortality among patients with 25 (OH) D deficiency (24.1% versus 8.6%) and 25 (OH) D insufficiency (12.2% versus 7%). However, in patients with normal levels of 25 (OH) D, the observed mortality was lower than predicted (4.4% versus 8%).

Arnson Y, Gringauz I *et al*[24] study indicated that survival of patients with vitamin D deficiency was significantly shorter than those whose vitamin D concentration was > 20 ng/ml (P < 0.05); the average survival time was 15.3 ± 12.4 days for vitamin D deficient patients compared with 24.2 ± 16.5 days among those with normal vitamin D levels.

Megan A Rech, Todd Hunsaker *et al*[22] conducted a study suggesting vitamin D deficiency (odds ratio, 2.70; 95% CI, 1.39-18.80; P =.02) were independently associated with increased 30-day mortality.

After multiple logistic regression analysis to all the confounding factors, high APACHE II score and endotracheal intubation rate were found to be independent predictors of mortality in patients with severe sepsis.

Conclusion :

1) The prevalence of vitamin D deficiency in severe sepsis is found to be 76%.
2) Low concentration of serum vitamin 25 (OH) D level in severe sepsis was significantly associated with female gender, respiratory and urinary system involvement, APACHE II score, increased duration of hospital stay, endotracheal intubation rate, duration of mechanical ventilation and higher mortality in severe sepsis especially when the 25 (OH) D level fell below 20 ng/ml.

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