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Predictive capacity of vitamin D and HDL levels alone and in combination for mortality in critically ill patients.

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ABSTRACT

INTRODUCTION: Vitamin D and HDL (high density lipoprotein) levels have potential to be used as an early and simple predictor of morbidity and mortality in critically ill patients. The aim of the study was to determine the predictive capacity of vitamin D and HDL levels alone and in combination for mortality in critically ill patients.

MATERIALS AND METHODS: Prospective observational study involving 302 patients admitted to an intensive care unit (ICU). Blood samples were obtained within the initial 24 hours of admission to assess vitamin D and HDL levels. Vitamin D levels of >20 ng/ml were considered non-deficient and ≤ 20 ng/mL considered deficient. HDL levels >30 mg/dl were considered normal HDL and <30 mg / dl were considered low HDL. The study collected data on various parameters including the APACHE II score at the ICU admission, SOFA scores throughout the ICU stay, 28-day mortality, as well as the requirement for mechanical ventilation, inotropic support, and renal replacement therapy.

RESULTS: Of 302 patients, 102 (33.77%) had mortality in 28 days. While analysing the predictive capacity of vitamin D and HDL alone and in combination for mortality at 28 days, the AUC (Area Under the Curve) was 0.667 (95% CI 0.610 TO 0.720), 0.673 (95%CI 0.617 TO 0.725), 0.628 (95% CI 0.571 TO 0.683) respectively. The vitamin D level 12 ng/ml and the HDL level 29 mg/dl were found to have a statistically significant association with mortality. P value <0.001.

CONCLUSIONS: The study showed that vitamin D and HDL levels alone and in combination have a significant association with mortality in critically ill patients.

KEY WORDS: Intensive care unit, high-density lipoprotein, mortality, vitamin D.

INTRODUCTION

The intensive care unit (ICU) is a challenging and complex unit of the healthcare delivery system. Several factors, including structure, organisation, and management, can influence ICU performance. To assess the impact of these factors, careful assessment of care components [1]. Mortality evaluation is an integral part of the critical care unit both for improved management and prognostication. Current mortality prediction models and scoring systems for intensive care unit patients generally require various parameters [2]. Vitamin D and HDL (high-density lipoprotein) levels have the potential to be used as an early and simple predictor of morbidity and mortality in critically ill patients [3,4]. These parameters can be used in the ICU and peripheral hospital settings due to the ease of availability. Vitamin D is a lipid-soluble vitamin which play an important role in the homeostasis of calcium, magnesium and phosphate [5]. In addition to classical functions, several non-classical functions have been suggested for vitamin D that are related to the presence of alpha-1-hydroxylase and vitamin D receptors in many body tissues. Vitamin D is also involved in the regulation of the immune system and also controls the functioning of the cardiovascular system and central nervous system. Vitamin D regulates both the innate and adaptive immune systems. Vitamin D deficiency leads to immune dysregulation and has been proposed as an underlying pathogenic mechanism for infections. Its deficiency has been found to be associated with increased markers of systemic inflammation associated with multiorgan failure. It is acclaimed that any critical disease affects the internal milieu of the body and can alter the reserves of vital nutrients and minerals of the body. Nutrition is usually inadequate in these patients, and this may further aggravate deficiencies. Vitamin D deficiency can hinder immune and metabolic functions in severely ill patients, leading to worse outcomes [6,7].

HDL represents a family of lipoprotein particles characterised by their ability to transport cholesterol from peripheral tissues back to the liver that confers a protective cardiovascular effect. In addition to its role in cholesterol metabolism, HDL also appears to emerge as relevant players in both innate and adaptive immunity [8]. They also appear to possess pleiotropic properties, including anti-inflammatory, antiapoptotic, or antioxidant functions. It has been found that lipoproteins bound to lipopolysaccharide and neutralize it further leading to enzyme incorporation, including paraoxonase and platelet-activating factor acetylhydrolase, inhibition of endothelial cell adhesion and stimulation of endothelial nitric oxide [9]. In addition, vitamin D and HDL levels are measured routinely in the ICU and would not cause any additional intervention or financial burden to patients. Despite advancements in the medical sciences, critically ill patients still face high risks of mortality and morbidity, prompting ongoing debate on the impact of factors like vitamin D and HDL on illness severity and clinical outcomes. Identifying and managing modifiable risk factors is crucial for improving outcomes in critically ill patients.

The purpose of the study was to determine the predictive capacity of vitamin D and HDL levels alone and in combination for mortality in critically ill patients.

MATERIALS AND METHODS

After obtaining approval from the institutional ethics committee (*IEC/ABVIMS/RMLH/598*) and the Clinical Trial Registry of India (*CTRI/2021/08/036028*), the prospective observational study was conducted. Inclusion criteria consisted of patients with ICU stays exceeding 48 hours. Exclusion criteria included refusal of consent, age under 18 years, pre-ICU admission cardiac arrest resuscitation prior to admission to the ICU, pregnancy or lactation, preexisting use of multivitamin or nutraceutical supplements, chronic malabsorption syndrome or diarrhoea, cancer diagnosis, and ongoing statin therapy. The sample size was calculated using a study by Moraes RB et al. [3] The area under the curve (AUC) of Vitamin D in the cited study was 0.6. As there is no previous study on HDL, we assumed a similar AUC for HDL- 0.6. For α-level 0.05 and β-level 0.10 (power is 90%) and using the AUC levels for vitamin D and HDL, the minimum sample size was found to be 275. Assuming a dropout rate of 10%, the final sample size was calculated to be 302.

In this study, we included conscious and unconscious patients admitted to an intensive care unit according to inclusion and exclusion criteria after obtaining approval from the institutional ethics committee. The following data were collected during the study period- Demographic data such as age, sex, weight, comorbidities & admission category. After the initial clinical evaluation and investigations, the patient, the following scores were taken - Acute Physiology and Chronic Health Evaluation (APACHE) II scoring systems on admission and alternate day SOFA score (Sequential Organ Failure Assessment). Data on morbidities during ICU stay (mechanical ventilation, use of inotropes / vasopressors and Renal Replacement Therapy) and all cause mortality were collected. Blood samples were drawn for vitamin D and HDL levels in the first 24 hours of ICU after initial resuscitation of the patient. Vitamin D levels of >20ng/dl were considered non-deficient. For HDL cut off of >30 mg/dl was taken. We studied the predictive power of vitamin D and HDL levels for mortality alone and in combination. Clinical practices were not changed or modified for study purposes. The primary objective of this study was to assess the ability of vitamin D and HDL levels alone and in combination to predict mortality at 28 days in critically ill patients. Secondary objectives of this study were to assess association of vitamin D and HDL levels with need for mechanical ventilation of Inotropes/Vasopressors support, the need for renal replacement therapy.

In statistical analysis categorical variables were performed in the form of number and percentage (%). On the other hand, the quantitative data was presented as the means ± SD. The associations of the variables that were qualitative in nature were analysed using the Chi-Square test. The receiver operating characteristic (ROC) curve was used to find the cut-off point, sensitivity, specificity, positive predictive value, and negative predictive value of vitamin D and HDL to predict mortality at 28 days. The DeLong test was used for the comparison of the area under the curve. Univariate logistic regression was used to find significant risk factors for mortality at 28 days. Data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 25.0. For statistical significance, the p value less than 0.05 was considered statistically significant.

RESULTS

The study cohort had 831 patients that included medical and surgical cases, as well as direct admissions / transfers to a multidisciplinary ICU. 529 patients were excluded from the study according to exclusion criteria. The main reason for exclusion was not being in the ICU for > 48 hours. In our study, only 302 patients were considered as a study group for analysis.

The study population of 302 consisted of a predominance of male population, that is 56.29% and females were 43.71%. The study consists of patients 18 to 85 years with mean age of 52.72 years. The maximum patients were in the age range of 61-70 years and contributed 28.48% of patients. The weight of the study patients ranges from 45-96 kg. With a Mean ± SD of 64.96 ± 11.1. (Table 1)

Table 1. Demography data.

Distribution of Gender of study subjects		
Gender	Frequency (n=302)	Percentage
Female	132	43.71%
Male	170	56.29%
Distribution of age(years) of study subjects		
Age (years)	Frequency (n=302)	Percentage
18-30	27	8.94%
31-40	41	13.58%
41-50	57	18.87%
51-60	69	22.85%
61-70	86	28.48%
>70	22	7.28%
Mean ± SD	52.72 ± 14.3	
Descriptive statistics of weight(kg) of study subjects		
Weight (kg) (Mean ± SD)	64.96 ± 11.1	

In the study, out of the total of 302 patients admitted to the ICU for >48 hours 221 (73.18%) had vitamin D deficiency. While 81 patients (26.82%) had normal levels of Vitamin D. The range of vitamin D levels were from 5-38 ng/ml, with Mean ± SD of 16.23 ± 6.72. Out of 302 patients, 133 (44.04%) had low HDL levels and 169 (55.96%) were having normal HDL levels. The range of HDL levels in the patients was 8-54 mg/dl, with Mean ± SD of 32.35 ± 9.94 (Table 2). Of 302 patients, 102 (33.77%) had mortality in 28 days. While analysing the predictive ability of vitamin D and HDL for 28 days' mortality, the AUC was 0.667 (95% CI 0.610 TO 0.720) and 0.673 (95%CI 0.617 TO 0.725), respectively. The receiver operating characteristic (ROC) curve was used to find the cut-off point, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of vitamin D and HDL to predict mortality at 28 days.

The DeLong et al. test was used for comparison of area under curve. Although the AUC for the combination was 0.628 (95% CI 0.571 TO 0.683). Vitamin D levels had a sensitivity and specificity of 51.96% and 78%, while HDL levels had a sensitivity and specificity of 60.78% and 67%. When both of them were combined, the sensitivity was reduced to 40.2% and the specificity increased to 85.5%. With a diagnostic precision of vitamin D of 69.21% and HDL of 64.90%. When both were combined, the diagnostic accuracy came out to be 70.20%. Vitamin D and HDL alone and in combination were found to have a statistically significant association with mortality. P-value <0.001 (Table 3, Figure 1).

Table 2. Distribution of vitamin D and HDL levels.

VITAMIN D LEVELS Distribution of vitamin D levels(ng/mL) of study subjects			HDL LEVELS Distribution of HDL levels(mg/dL) of study subjects		
Vitamin D levels (ng/mL)	Frequency (n=302)	Percentage	HDL levels(mg/dL)	Frequency (n=302)	Percentage
Vitamin D deficient {<=20 ng/mL}	221	73.18%	Low HDL {<=30 mg/dL}	133	44.04%
Vitamin D non deficient{>20 ng/mL}	81	26.82%	Normal HDL {>30 mg/dL}	169	55.96%
Mean ± SD	16.23 ± 6.72		Mean ± SD	32.35 ± 9.94	

SD: Standard Deviation

Table 3. Correlation of vitamin D, HDL and their combination to predict mortality at 28 days.

Variables	Vitamin D	HDL	Vitamin D and HDL
AUC ROC	0.667	0.673	0.628
Standard Error	0.0345	0.034	0.0274
95% Confidence interval	0.610 to 0.720	0.617 to 0.725	0.571 to 0.683
P value	**<0.001**	**<0.001**	**<0.001**
Cut off	≤ 12 ng/ml	≤ 29 mg/dl	-
Sensitivity (95% CI)	51.96% (41.8 - 62.0%)	60.78% (50.6 -70.3%)	40.2% (30.6 - 50.4)
Specificity (95% CI)	78% (71.6 - 83.5%)	67% (60.0 - 73.5%)	85.5% (79.8 - 90.1)
PPV (95% CI)	54.6% (44.2 - 64.8%)	48.4% (39.5 - 57.4%)	58.6% (46.2 - 70.2%)
NPV (95% CI)	76.1% (69.7 - 81.8%)	77% (70.0 - 83.0%)	73.7% (67.5 - 79.3%)
Diagnostic accuracy	69.21%	64.90%	70.20%

Data analysed by ROC curve, CI: Confidence interval and DeLong test. p-value < 0.05 Significant.

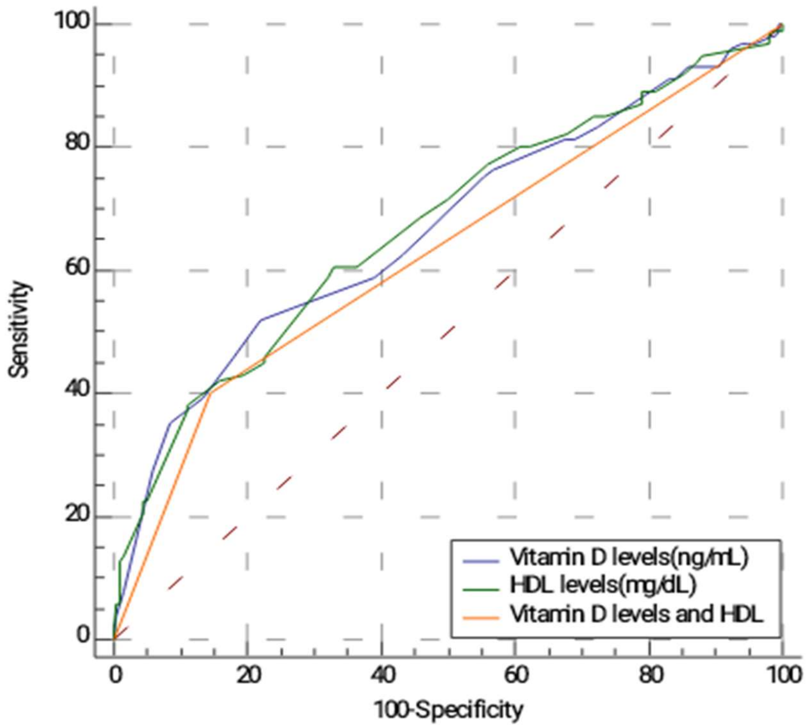

Figure 1. Receiver operating characteristic curve of vitamin D levels(ng/mL), HDL levels(mg/dL) and their combination to predict ICU mortality.

Table 4. Univariate logistic regression to find significant risk factors for ICU mortality.

Variable	Beta coefficient	Standard error	P value	Odds ratio	Odds ratio Lower bound (95%)	Odds ratio Upper bound (95%)
Age(years)	-0.003	0.008	0.703	0.997	0.980	1.013
Weight(kg)	0.006	0.011	0.557	1.007	0.985	1.029
Vitamin D levels(ng/mL)	-0.085	0.021	**<0.001**	0.918	0.881	0.957
HDL levels(mg/dL)	-0.065	0.014	**<0.001**	0.937	0.912	0.962
Vitamin D(ng/ml) and HDL(mg/dl)	1.343	0.264	**<0.001**	3.830	2.283	6.427
APACHE II at the time of admission	0.141	0.028	**<0.001**	1.152	1.090	1.217
Mean SOFA	0.379	0.046	**<0.001**	1.461	1.335	1.598

Data analysed by odds ratio. P < 0.05 is significant.

In univariate analysis, vitamin D, HDL levels and their combination have statistically significant association with mortality, similar to APACHE II on admission and mean SOFA of ICU stay. P value <0.001 (Table 4). Upon analysis of the association of Vitamin D and morbidity, the need for renal replacement therapy had a statistically significant association with morbidity; While with the use of ventilator and Ionotropic use, no statistically significant association was found. No statistically significant association of HDL and morbidity was found with the need for renal replacement therapy, the use of ventilator and Inotropes (Table 5).

Table 5. Association of Vitamin D and HDL levels with morbidity.

Morbidity	Vitamin D deficient {<=20 ng/mL} (n=221)	Vitamin D non deficient {>20 ng/mL} (n=81)	Total (n=302)	P value	Low HDL {<=30 mg/dL} (n=133)	Normal HDL {>30 mg/dL} (n=169)	Total (n=302)	P value
Renal replacement therapy	36 (16.29%)	6 (7.41%)	42 (13.91%)	0.048	19 (14.29%)	23 (13.61%)	42 (13.91%)	0.866
Need of mechanical ventilaton	181 (81.90%)	62 (76.54%)	243 (80.46%)	0.298	108 (81.20%)	135 (79.88%)	243 (80.46%)	0.774
Inotropes use	133 (60.18%)	53 (65.43%)	186 (61.59%)	0.406	86 (64.66%)	100 (59.17%)	186 (61.59%)	0.330

DISCUSSION

The study was carried out in 302 patients, of which females constituted 43.71% and the rest 56.29% were men. The mean age of the patients was 52.72 years. In the study by Derakhshanian H. et al. the mean age group of patients having vitamin D deficiency was 63 years and in the group without deficiency was 60 years. The results were not significant in terms of age distribution [10]. Lee SH et al. in their study included 117 patients with a mean age of 62 years, while the gender distribution was similar in both groups. [11]. Hence, the demographic distribution of vitamin D and HDL deficiency has been found to be not significant.

In this study, the predictive ability of vitamin D levels for mortality was found to be moderate (AUC=0.667, 95% CI 0.610 TO 0.720). Vitamin D was a significant predictor of mortality at a cut-off point of 12 ng/ml. The sensitivity and specificity were 51.96% and 78%, respectively. The study by Venkatram S et al. found that vitamin D deficiency was associated with higher mortality [12]. Similarly, Remmelts et al. also concluded that Vitamin D status is an independent predictor of 30-day mortality and adds prognostic value to other biomarkers and prognostic scores [13]. Lange N et al. study 23,603 patients and concluded vitamin D levels are associated with the odds of all-cause patient mortality at 30 days after hospitalisation [14]. Hence, in accordance with the above mentioned studies, it favours the results in this study.

HDL levels were found to have a statistically significant association with mortality. HDL predictive ability of HDL was moderate (AUC=0.673, 95% CI 0.617 TO 0.725). The sensitivity and specificity were 60.78% and 67%, respectively. Cirstea M et al. found that plasma HDL levels are the best prognostic marker for adverse outcomes in ICU patients [15]. Guo X. et al. conducted a study in 3384 patients and found that serum HDL-C concentrations were significantly lower for non-survivors than for survivors [16]. Similar to this study, Tanaka et al. found a significant association of low HDL value on admission with mortality. Compared to this study, they also evaluated HDL trends, where they found increasing trends of HDL levels to be associated with clinical improvement [17]. Vitamin D deficiency was shown to be associated with higher levels of LDL-C, TG, and Apo B., while higher vitamin D level was shown to be associated with a favorable lipid profile, such as high levels of HDL and Apo A. [18]. In this study, the combination of vitamin D and HDL was found to have statistically significant association with mortality (AUC=0.628, 95% CI 0.571 TO 0.683). The sensitivity and specificity were 40.2% and 85.5%, respectively.

In this study, 80.4% of patients needed mechanical ventilatory support of a total 302. In the vitamin D deficient group, 81.90% and 76.54% of the non-deficient vitamin D group required mechanical ventilatory support. Although vitamin D deficiency leads to an increased need for mechanical ventilation, the results were found to be statistically not significant. Vassiliou AG. et al. found that vitamin D deficiency leads to a longer mechanical ventilation [19]. Another study by Derakhshanian H. et al. showed that low vitamin D levels leads to higher duration of mechanical ventilation [10]. 40.04% (n = 133) of the patients had low HDL and out of them 81.20% (n=108) needed mechanical ventilatory support during hospital stay. On the other side, 135 patients out of 169 patients (that is, 79.88%) with HDL level greater than 30 mg/dl needed ventilatory support. The results were found to be statistically nonsignificant. Tanaka S. et al. in their study found no significant correlation between HDL levels and need for mechanical ventilation [20].

In this study, 16.29% had vitamin D levels below 20 ng/ml needed renal replacement therapy compared to 7.41% patients in the normal vitamin D group (p=0.05). The results were found to be statistically significant. Similarly to our results, Zapatero et al. and Shen H. et al. found that vitamin D deficiency leads to a higher incidence of acute kidney injury [21,22]. In the current study, 14.29% of patients with low HDL needed renal replacement therapy, while 13.61% patients in normal HDL group (p=0.8). The results were found to be statistically not significant. However, Roveran et al. in their study found that patients with low HDL levels had a significantly higher frequency of AKI compared to those with high HDL [23]. 186 patients required inotropic support out of 302 patients. 64.66% of the patients belonged to the low HDL group and 59.17% of the patients with normal HDL. The results were found to be statistically not significant. A total of 61.59 % of the patients required inotropic support during the study, of them 60.18% belong to vitamin D deficient group and 65.43% belong to the vitamin D sufficient group. The results were found to be statistically not significant. Loni R. et al. in their study found that low vitamin D leads to higher vasopressor requirements [24].

The limitations include its small sample size and short duration, along with recruitment exclusively from a single tertiary care hospital. Future research could improve precision and generalizability by recruiting participants from multiple tertiary care hospitals. Additionally, rather than relying solely on single measurements of vitamin D and HDL at admission, exploring serial values and trends may offer deeper insights into associations and prognostic implications. Consequently, larger-scale studies conducted over longer periods are essential to generate more robust findings.

CONCLUSIONS

The study showed that vitamin D and HDL levels alone and in combination have a significant association with mortality in critically ill patients. Maintaining sufficient levels of vitamin D and HDL 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 for adequate vitamin D and HDL status in their prevention of mortality.

SUPPLEMENTARY INFORMATION

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