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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/20027
DOI URL: http://dx.doi.org/10.21474/IJAR01/20027

RESEARCH ARTICLE

THE CORRELATION BETWEEN VITAMIN D LEVELS AND SEPSIS: EXPLORING ITS IMPACT ON PATIENT OUTCOMES

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Manuscript Info

Manuscript History
Received: 07 October 2024
Final Accepted: 09 November 2024
Published: December 2024

Key words:-
Sepsis, Vitamin D, APACHE II, SAPS II, GCS

Abstract

Background: Sepsis continues to be the primary cause of death and ICU admissions worldwide. Not only is vitamin D important for healthy bones, but it also has a major impact on immune system regulation. It is yet unknown how vitamin D levels relate to the severity of sepsis, despite data linking vitamin D insufficiency to poor outcomes in critically sick patients.

Aims & Objectives: This study aimed to examine the correlation between vitamin D levels and the severity of sepsis in patients, assessing whether vitamin D deficiency impacts patient outcomes.

Methods: From June 2023 to May 2024, a prospective observational research was carried out at a tertiary care facility in Northern India. Enrolled were 273 individuals who had been hospitalized with septic shock, severe sepsis, or sepsis. The CLIA technique was used to test vitamin D levels, and the APACHE II, SAPS II, and GCS scores were used to gauge the severity of sepsis. ANOVA, the Student's t-test, and linear regression were used in the statistical study.

Results: Patients with lower vitamin D levels exhibited lower APACHE II scores, but differences in SAPS II and GCS scores were not statistically significant. Discharged patients had significantly lower SAPS II scores compared to expired patients (P = 0.038). No significant difference in GCS scores was found between the two groups (P = 0.933).

Conclusions: This study suggests that vitamin D deficiency may influence sepsis severity, as measured by APACHE II scores, but has no significant impact on SAPS II or GCS scores. Further research is needed to explore the potential role of vitamin D supplementation in improving sepsis outcomes.

Introduction:-

Sepsis, a leading cause of mortality and intensive care unit (ICU) admissions globally, imposes a significant healthcare burden both in terms of lives lost and economic cost.[1]As our knowledge of the immune system expands, focus has switched to investigating the function of micronutrients in immunological regulation, with vitamin D

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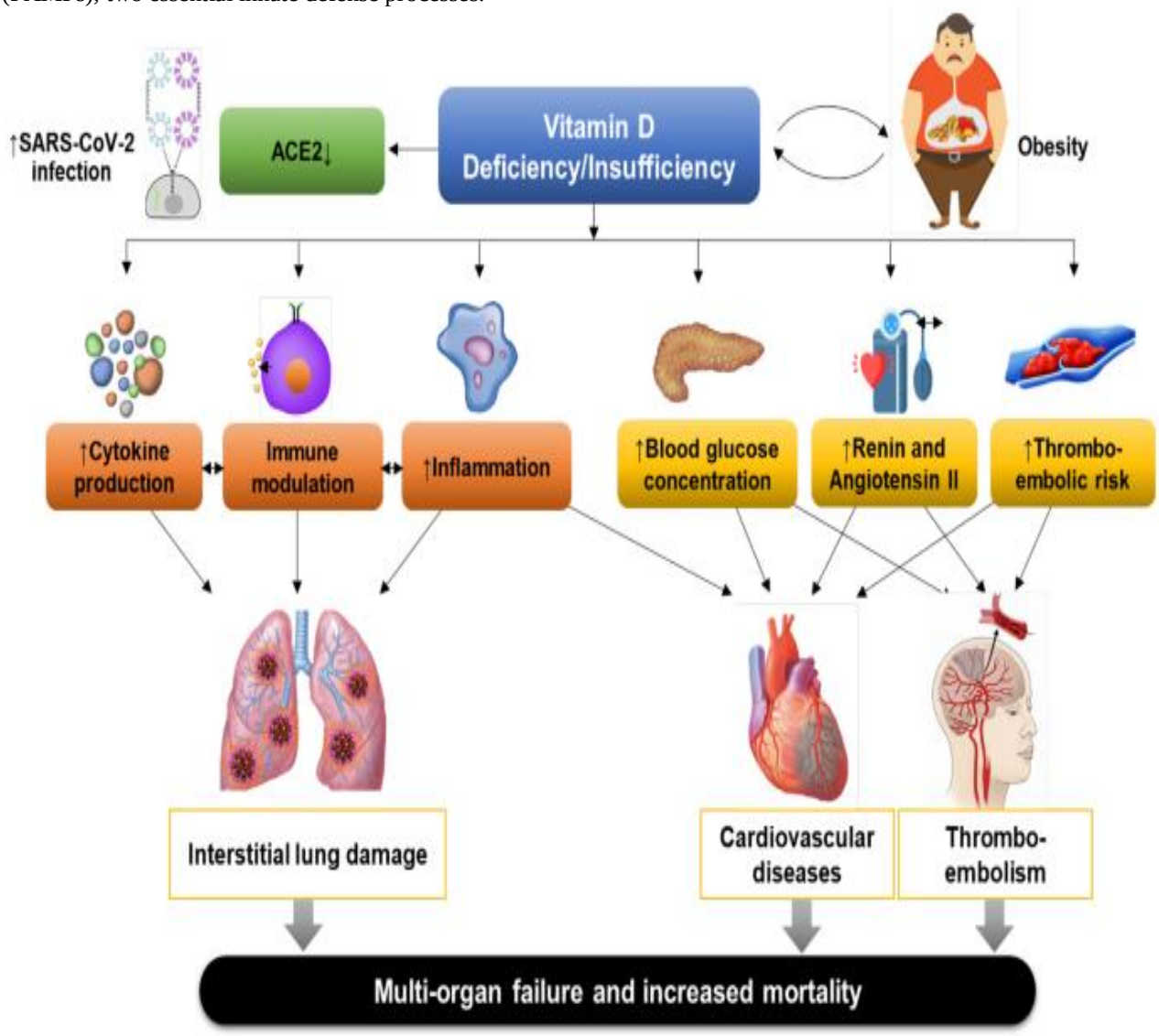
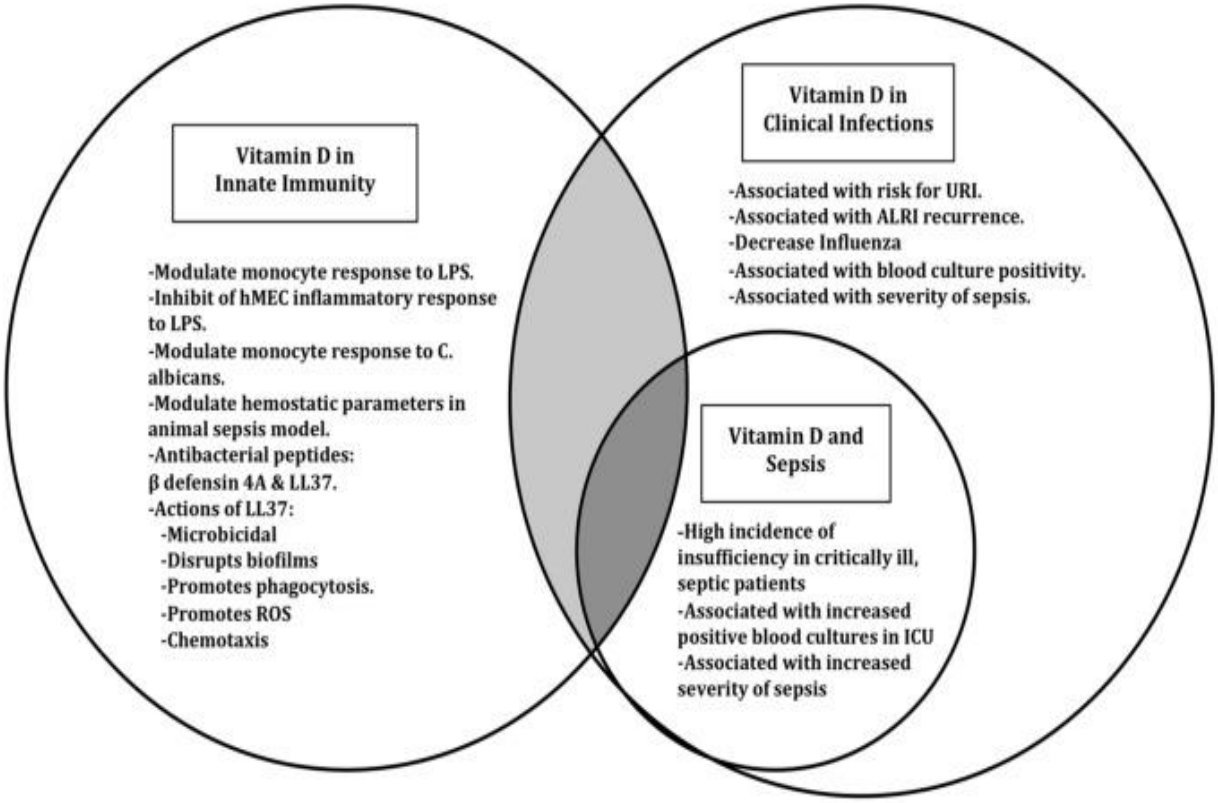
emerging as a critical component. Although vitamin D is well known for helping to maintain calcium homeostasis and bone health, its effects are not limited to the skeletal system. In actuality, vitamin D—particularly the two forms, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol)—is essential for regulating immunological function. For most people, the major source of vitamin D is still cutaneous synthesis, which is stimulated by sunshine.[2]

The immune system has been shown to benefit from vitamin D, especially when it comes to the control of both innate and adaptive immunity. Through affecting T and B lymphocyte activity, it has been demonstrated to enhance the innate immune response while regulating adaptive immunity.[3]Vitamin D's importance in immune control is further demonstrated by the identification of vitamin D receptors (VDRs) on almost all immune cells, including activated T cells, neutrophils, macrophages, and dendritic cells.[4] According to research, vitamin D aids in pathogen identification by activating pathogen recognition receptors (PRRs) and pathogen-associated molecular patterns (PAMPs), two essential innate defense processes.[5,6]



This figure shows the impact of Vitamin D deficiency

The measurable form of vitamin D in clinical settings, 25-hydroxyvitamin D (25-OH D), provides insight into a patient's vitamin D status, as it has a relatively long half-life, making it a reliable marker. Given the crucial role of vitamin D in immune function, it is plausible to hypothesize that vitamin D levels may influence sepsis outcomes. [7,8]



This figure shows the role of Vitamin D in Innate Immunity, Clinical Infections, and Its Association with Sepsis

This study aims to investigate the correlation between vitamin D levels and sepsis, offering potential insights into whether optimizing vitamin D status could improve patient outcomes and mitigate the devastating effects of sepsis.

Materials and Methods:-

Study Design

This prospective observational study was carried out at the Department of Medicine at a tertiary care facility in Northern India between June 2023 and May 2024. The purpose of the study was to investigate the relationship between sepsis severity and vitamin D levels.

The criteria for inclusion:

All persons hospitalized to the intensive care unit (ICU) or emergency department with sepsis, severe sepsis, or septic shock who were 18 years of age or older were included in the research. The informed permission of all participants was obtained, and ethical approval was acquired from the local ethics commission.

The criteria for exclusion:

Excluded from the research were patients who did not provide their agreement to participate, were pregnant, or had a diagnosis of TB, chronic liver disease (CLD), or chronic kidney disease (CKD).

Vitamin D Measurement

Vitamin D levels were quantitatively assessed using the CLIA method in the Biochemistry Department of F.H. Medical College, Agra, with the DiasminLiasonanalyzer. The Endocrine Society's definition of vitamin D insufficiency was 25(OH) D levels less than 30 ng/mL.

Data Collection

Data were collected on patient demographics, including age, sex, blood pressure, pulse rate, temperature, and comorbidities. Blood samples were drawn for CBC, LFT, KFT, and serum vitamin D levels.

Statistical Analysis

It was reported that continuous values were mean ± standard deviation, and categorical variables were percentages. Analyzing categorical data was done with the Chi-square test or Fisher's exact test; for continuous variables, the Student's t-test or ANOVA was utilized. The association between sepsis severity and vitamin D levels was evaluated using APACHE II and MEDS scores through univariable linear regression analysis.

Results:-

Table 1:- Sociodemographic Characteristics of Study Participants.

Sociodemographic Characteristic	Value
Total eligible patients	280
Total Patients Enrolled	273
Patients Excluded	7 (CKD, CLD, TB)
Mean Age (years)	50 ± 14.69
Gender	Not specified in given data
Comorbidities	CKD, CLD, TB (Excluded)

The sociodemographic information of the research participants is shown in Table 1. After 7 individuals with chronic illnesses such as CKD, CLD, and TB were excluded from the research, 273 participants were included in the trial. The participants' mean age was 50 ± 14.69 years.

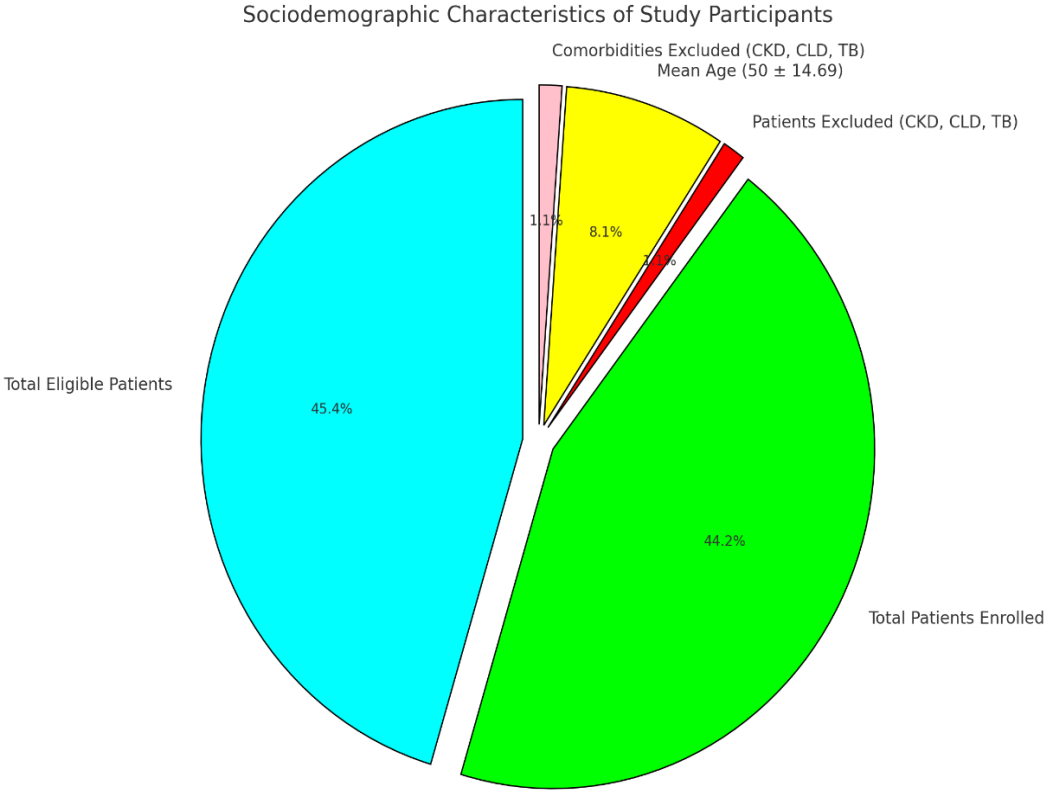


Table 2:- Mean APACHE II Scores by Vitamin D Levels.

Vitamin D Levels	Mean APACHE II Score	Standard Deviation	P-Value
Deficiency	15.79	6.18	0.044
Insufficiency	16.57	2.51	0.044
Normal	20.38	8.46	0.044

The correlation between vitamin D levels and APACHE II scores is seen in Table 2. The mean APACHE II score was lower in patients with vitamin D insufficiency (15.79 ± 6.18) than in those with normal vitamin D levels (20.38 ± 8.46). There was a statistically significant difference in scores between the groups (P = 0.044).

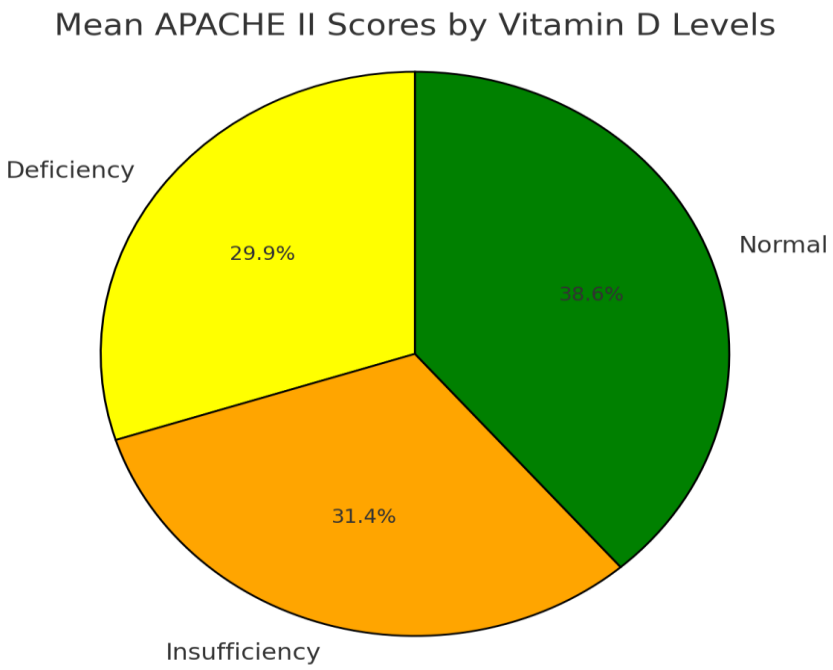


Table 3:- Mean SAPS II Scores by Vitamin D Levels.

Vitamin D Levels	Mean SAPS II Score	Standard Deviation	P-Value
Deficiency	34.29	12.22	0.654
Insufficiency	33.71	10.64	0.654
Normal	35.63	17.80	0.654

The mean SAPS II scores for patients with varying amounts of vitamin D are displayed in Table 3. Although there is a little range in the scores, the differences were not statistically significant (P = 0.654), with individuals with normal Vitamin D levels having the highest mean score (35.63).

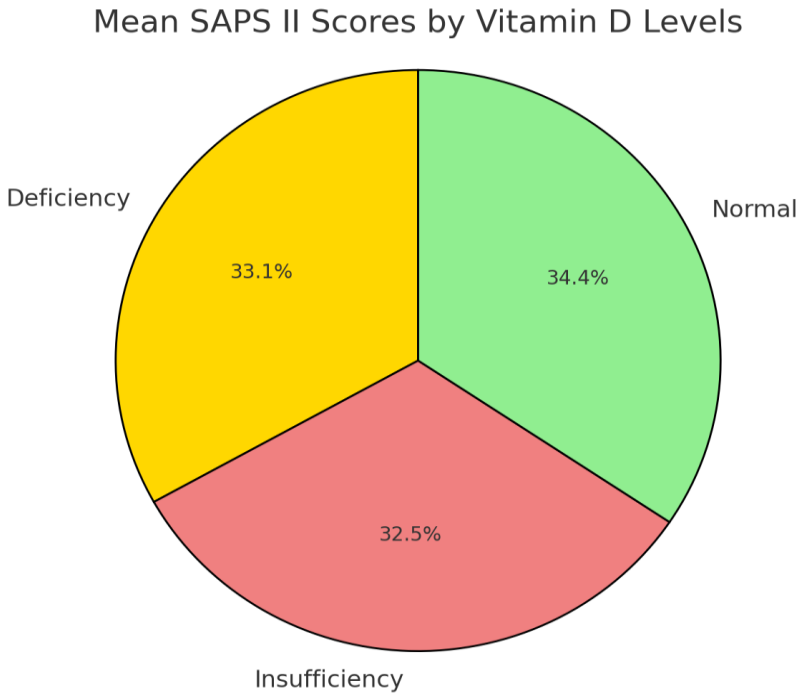


Table 4:- Mean GCS Scores by Vitamin D Levels.

Vitamin D Levels	Mean GCS Score	Standard Deviation	P-Value
Deficiency	11.32	4.76	0.933
Insufficiency	11.86	3.76	0.933
Normal	10.25	4.37	0.933

Table 4 highlights the mean GCS scores across different Vitamin D levels. While patients with Vitamin D insufficiency had slightly higher mean GCS scores (11.86), the difference between groups was not statistically significant (P = 0.933).

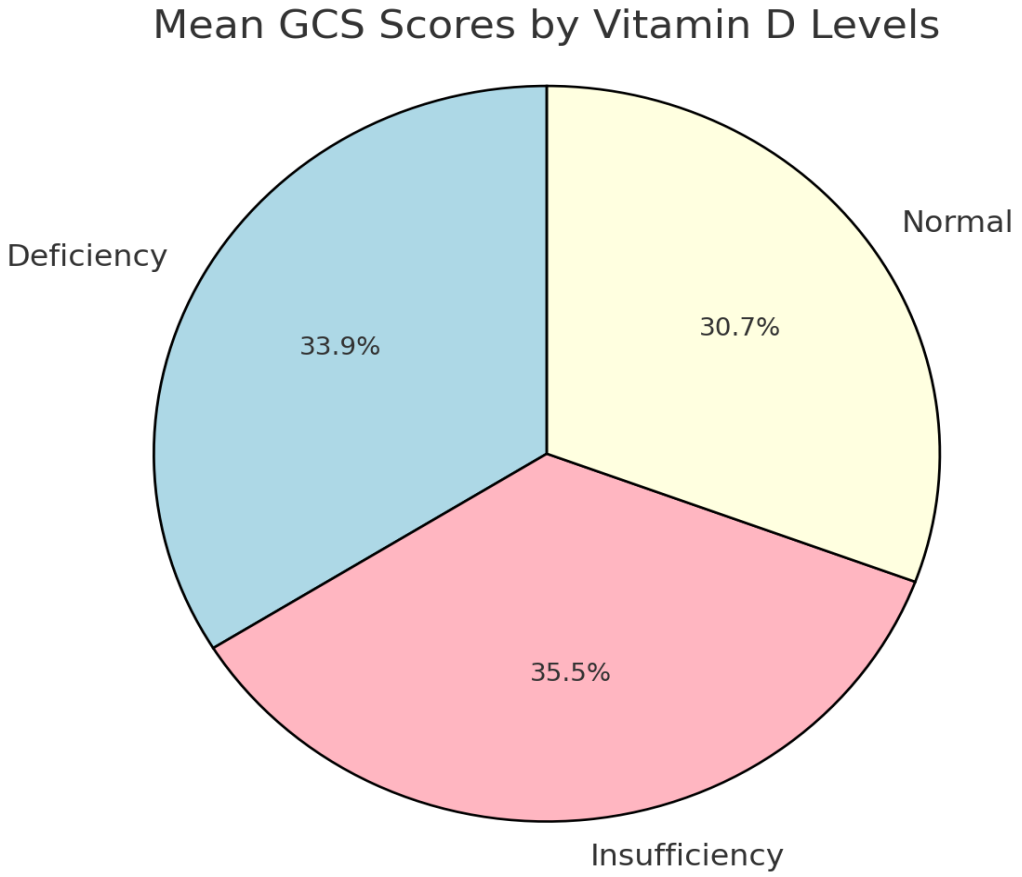
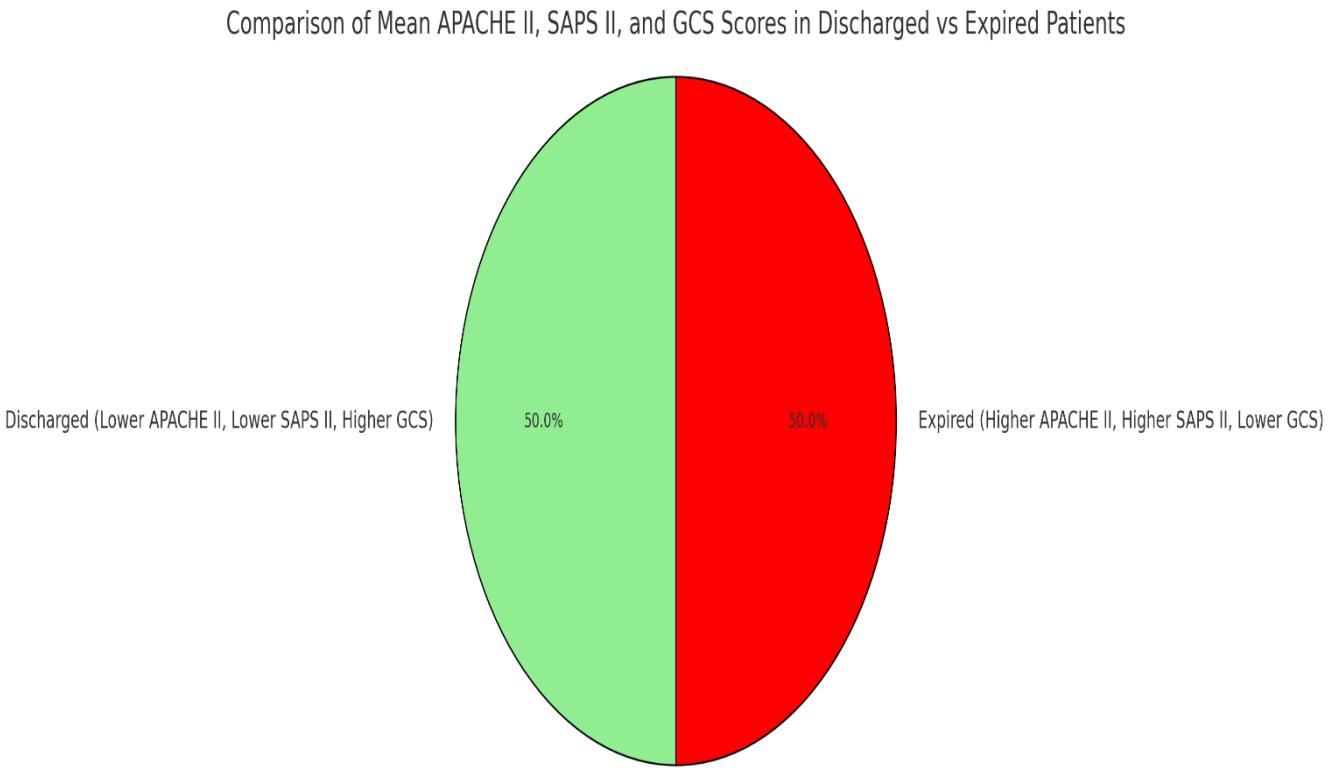


Table 5:- Comparison of Mean APACHE II and SAPS II Scores in Discharged vs Expired Patients.

Outcome	Mean APACHE II Score	Mean SAPS II Score	Mean GCS Score
Discharged	Lower	Lower	Higher
Expired	Higher	Higher	Lower
P-Value (SAPS II)	-	0.038	0.933

Table 5 compares the outcomes between discharged and expired patients. Patients who expired had higher mean APACHE II and SAPS II scores, while discharged patients had higher mean GCS scores. The difference in SAPS II scores was statistically significant (P = 0.038).



Discussion:-

In our study, we enrolled 273 out of 280 eligible patients, excluding 7 with comorbidities like CKD, CLD, and TB. The mean age of participants was 50 ± 14.69 years, with no gender data specified. Excluding patients with CKD, CLD, and TB highlights their potential impact on vitamin D levels and sepsis outcomes.**Holick et al.[9] (2011)** discussed the importance of excluding patients with chronic diseases when studying vitamin D's role in immune responses, though they did not specifically focus on CKD or CLD exclusion. They emphasized that vitamin D deficiency should be studied in populations with minimal comorbidities to accurately assess its impact on immune function.

In our study, we found that patients' APACHE II scores varied with vitamin D levels. Those with deficiency had a score of 15.79 ± 6.18, insufficiency scored 16.57 ± 2.51, and patients with normal levels had the highest score of 20.38 ± 8.46. The differences were statistically significant (P = 0.044), suggesting a link between vitamin D levels and illness severity. **Holick et al.[9] (2011)** discussed the impact of vitamin D deficiency on overall health outcomes, particularly in immune function. While they did not directly study APACHE II scores, they observed that low levels of vitamin D are associated with worse clinical outcomes in individuals who are critically sick, indicating that sepsis and other severe illnesses may require the maintenance of appropriate vitamin D levels to modulate immune responses.Similarly, **Yamshchikov et al.[10] (2009)** conducted a systematic review on vitamin D's role in infectious diseases and emphasized its immunomodulatory function. Although they did not measure APACHE II scores specifically, these results are consistent with our study's finding that patients with vitamin D insufficiency had lower APACHE II ratings, suggesting a correlation between lower vitamin D levels and more severe illness outcomes.

We also found that SAPS II scores were similar across varying vitamin D levels. Patients with deficiency had a score of 34.29 ± 12.22, insufficiency scored 33.71 ± 10.64, and those with normal levels scored 35.63 ± 17.80. According to SAPS II scores, there may not be a direct correlation between vitamin D levels and the severity of the disease, since the differences were not statistically significant (P = 0.654).**Holick et al.[9] (2011)** provided comprehensive guidelines on the evaluation and treatment of vitamin D deficiency, emphasizing that vitamin D plays a crucial role in immune function and health outcomes in critically ill patients. Although their study did not specifically measure SAPS II scores, They came to the conclusion that individuals who are severely sick and have a vitamin D deficit would have worse clinical outcomes. This is consistent with our study's focus on evaluating

vitamin D levels in a critically ill population, although no direct relationship with SAPS II scores was found in this case.**Yamshchikov et al.[10] (2009)**, in their systematic review of randomized controlled trials, explored the role of vitamin D in preventing and treating infectious diseases. While their study did not directly examine SAPS II scores, They discovered that giving patients with infectious disorders vitamin D supplements led to better clinical results. According to their research, vitamin D may be involved in regulating immunological responses, potentially influencing disease severity, although further studies are needed to establish this connection with SAPS II scores.**Zhao et al.[11] (2012)** conducted a study on serum 25-hydroxyvitamin D levels and all-cause and cardiovascular disease mortality among adults in the US. They found that low vitamin D levels were associated with increased mortality, particularly in patients with hypertension. While this study did not examine SAPS II scores or critically ill patients, it underscores the broader impact of vitamin D deficiency on patient outcomes.

In our study, we found that GCS scores were similar across different vitamin D levels. Patients with deficiency had a score of 11.32 ± 4.76, insufficiency scored 11.86 ± 3.76, and normal levels scored 10.25 ± 4.37. According to GCS, vitamin D levels had no discernible effect on neurological state, since the changes were not statistically significant (P = 0.933).**Holick et al.[9] (2011)** discussed the role of vitamin D in overall health and immune function, especially in critically ill patients. Although their study did not directly investigate GCS scores,they highlighted the link between worse clinical outcomes in individuals with severe illnesses and vitamin D insufficiency, which could extend to neurological assessments like GCS scores. However, the specific lack of statistical significance in our study's findings contrasts with Holick's broader conclusions about vitamin D's general influence on health outcomes.**Yamshchikov et al.[10] (2009)**, in their systematic review on vitamin D's role in the prevention and treatment of infectious diseases, noted the potential of vitamin D to modulate immune responses and influence disease severity. While their findings support the importance of vitamin D in overall health, they did not specifically examine neurological outcomes like GCS. This aligns with our study's findings that vitamin D levels may not have a direct influence on neurological status, as measured by GCS scores, but rather play a broader role in systemic health and disease progression.**Møller et al.[1] (2007)** explored the effect of 1,25-dihydroxy-vitamin D3 in experimental sepsis. They found that vitamin D improved survival rates and modulated immune responses in septic models, but the study did not report data on neurological outcomes like GCS scores. Our study's lack of significant findings in GCS scores suggests that while vitamin D plays a role in immune modulation and survival in critically ill patients, its direct influence on neurological status, as indicated by GCS, may be limited or require further investigation.

In our study, we found that discharged patients had lower APACHE II and SAPS II scores, while expired patients had higher scores. Discharged patients also had higher GCS scores. A significant difference was observed in SAPS II scores (P = 0.038), but not in GCS scores (P = 0.933), suggesting SAPS II is a better predictor of outcomes than GCS in this cohort. **Autier and Gandini et al.[12] (2007)** conducted a meta-analysis on vitamin D supplementation and mortality, reporting that vitamin D plays a role in improving outcomes in patients with critical illnesses. However, they did not specifically analyze APACHE II or SAPS II scores. Their findings support our study's observation that patients with higher severity scores tend to have poorer outcomes, though the relationship between vitamin D levels and these scores was not directly addressed in their analysis.**Holick et al.[9] (2011)** discussed the broader implications of vitamin D deficiency on health outcomes, particularly in critically ill patients. They highlighted that vitamin D deficiency is linked to poorer clinical outcomes, but did not directly study APACHE II or SAPS II scores. While their findings align with the general observation that vitamin D deficiency correlates with worse outcomes, they did not provide specific data on severity scores, which limits direct comparison with our study's findings.In conclusion, our study's results regarding the association between APACHE II, SAPS II, and patient outcomes add new insights to the existing literature. However, there is a gap in studies that specifically examine these severity scores in relation to vitamin D levels and patient mortality, indicating that more targeted research is needed to understand the interaction between these variables.

Conclusion:-

Globally, sepsis is a major cause of illness and death. When it comes to vitamin D reserves, a sizable portion of our population is either inadequate or deficient. Studies have demonstrated a detrimental effect on inpatient morbidity, mortality, and sepsis severity indicators in the patients. This emphasizes how crucial it is that people in general take enough vitamin D supplements. More research is required to show if vitamin D treatment in sepsis patients will change the course of their hospital stay and the morbidities that these patients with vitamin D deficiency encounter.

Recommendations:-

To further understand the relationship between vitamin D levels and sepsis outcomes, bigger, more varied populations should be the focus of future research. More light on vitamin D's potential as a treatment might come from randomized controlled studies examining the effects of supplementation in sepsis patients. In addition, more investigation is needed to determine how comorbidities affect the connection between vitamin D levels and the severity of sepsis.

Limitations

This study was limited by the exclusion of patients with chronic conditions like CKD, CLD, and TB, which may have affected the generalizability of the findings. The lack of gender data and potential variations in sunlight exposure were also not accounted for, which could have influenced vitamin D levels and patient outcomes.

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