Orjinal Araştırma **Van Sağ. Bil. Derg.** *2025; 18(1):65-70*
Original Research *https://doi.org/10.52976/vansaglik.1619928*

Association of Vitamin D and Magnesium Deficiencies with Clinical Outcomes in Sepsis

D Vitamini ve Magnezyum Eksiliklerinin Sepsisde Klinik Sonuçlarla İlişkisi

Suna Mehtap Yıldırım[1], Özgür Özmem[*2,3], Elif Oral Ahıskalıoğlu[2],*

Nazım Doğan[2,3], Hüsnü Kürşad[2]

[1] Bilecik Bozüyük State Hospital, Department of Anesthesiology and Reanimation, Bilecik, Türkiye

[2] Atatürk University School of Medicine, Department of Anesthesiology and Reanimation, Erzurum, Turkey, Türkiye

[3] Atatürk University Anethesiology Clinical Research Office, Atatürk University, 25240, Erzurum, Türkiye

Cited: Yıldırım SM, Özmen Ö, Oral Ahıskalıoğlu E, Doşan N, Kürşad H. (2024). Association of Vitamin D and Magnesium Deficiencies with Clinical Outcomes in Sepsis. *Van Sağlık Bilimleri Dergisi*, 18(1), 65-70.

ABSTRACT

Objective: This study aims to investigate the association of vitamin D and magnesium levels with the severity of sepsis and septic shock in intensive care unit patients.

Material and Method: A retrospective study was conducted in the ICU of a tertiary hospital, involving 299 sepsis patients admitted between January 2017 and January 2019. Patients' demographic data, vitamin D and magnesium levels, labarotory parameters, and clinical scores (APACHE II, SOFA, SAPS II) were collected at admission and discharge. Statistical analyses, including chi-square and correlation analysis, were performed to evaluate the association between these micronutrients and mortality.

Results: The results showed that while hypomagnesemia was associated with higher clinical severity scores, including APACHE II and SOFA ($p<0.05$), neither vitamin D nor magnesium levels were independently predictive of mortality. Magnesium deficiency correlated with worse clinical outcomes, ($p<0.05$) but its association with mortality remained inconclusive ($p>0.05$). Similarly, low vitamin D levels, though prevalent, did not significantly influence survival ($p>0.05$).

Conclusion: Vitamin D and magnesium levels were not independently associated with mortality in sepsis patients. However, magnesium deficiency was linked to higher severity scores, indicating its potential role in disease progression. Further research is needed to explore the therapeutic implications of correcting these deficiencies in critically ill patients.

Keywords: *Sepsis, Vitamin D, Magnesium, APACHE II, SOFA*

ÖZET

Giriş: Bu çalışmanın amacı yoğun bakım hastalarında D vitamini ve magnezyum düzeylerinin sepsis ve septik şokun şiddeti ile ilişkisini araştırmaktır.

Materyal ve Metot: Üçüncü basamak bir hastanenin YBÜ'sünde Ocak 2017 ile Ocak 2019 tarihleri arasında kabul edilen 299 sepsis hastasını kapsayan retrospektif bir çalışma yapılmıştır. Hastaların demografik verileri, D vitamini ve magnezyum düzeyleri, laboratuvar parametreleri ve klinik skorları (APACHE II, SOFA, SAPS II) başvuru ve taburculuk sırasında toplanmıştır. Bu mikro besin öğeleri ile mortalite arasındaki ilişkiyi değerlendirmek için ki-kare ve korelasyon analizi dahil olmak üzere istatistiksel analizler yapılmıştır.

Bulgular: Sonuçlar, hipomagnezeminin APACHE II ve SOFA dahil olmak üzere daha yüksek klinik ciddiyet skorlarıyla ilişkili olduğunu gösterirken ($p<0,05$), ne D vitamini ne de magnezyum seviyelerinin bağımsız olarak mortaliteyi öngörmediğini göstermiştir. Magnezyum eksikliği daha kötü klinik sonuçlarla ilişkilidir ($p<0.05$) ancak mortalite ile ilişkisi yetersiz kalmıştır ($p>0.05$). Benzer şekilde, düşük D vitamini düzeyleri yaygın olmasına rağmen sağkalımı önemli ölçüde etkilememiştir ($p>0.05$).

Sonuç: D vitamini ve magnezyum düzeyleri sepsis hastalarında mortalite ile bağımsız olarak ilişkili bulunmamıştır. Bununla birlikte, magnezyum eksikliği daha yüksek şiddet skorlarıyla bağlantılı olup, hastalığın ilerlemesindeki potansiyel rolüne işaret etmektedir. Kritik hastalarda bu eksikliklerin düzeltilmesinin terapötik etkilerini keşfetmek için daha fazla araştırmaya ihtiyaç vardır.

Anahtar kelimeler: *Sepsis, Vitamin D, Magnezyum, APACHE II, SOFA*

* *Corresponding author: Özgür Özmen. E-mail:* dr.ozgurozmen@yahoo.com.tr
ORCIDS: Suna Mehtap Yıldırım: 0000-0002-5675-0121, *Özgür Özmen*: 0000-0003-2014-0468, *Elif Oral Ahıskalıoğlı*: 0000-0003-1234-5973, *Nazım Doğan:* 0000-0001-6706-5085, *Hüsnü Kürşad*: 0000-0002-8602-8965

Received: 15.01.2025, Accepted: 18.04.2025 and Publeshed:30.04.2025

INTRODUCTION

Septic shock and sepsis are the primary causes of morbidity and mortality in intensive care patients. It creates a significant economic and health burden (Yealy et al., 2021). The annual death rate due to sepsis in the world constitutes 19.7% of all deaths (Rhee et al., 2019; Rudd et al., 2020). In patients in intensive care units; Despite all technological developments and renewed treatment protocols, high mortality rates are still observed (Angus and Van Der Poll, 2013). Prompt identification and management of sepsis are crucial, as it is a time-critical illness that requires early intervention to improve patient outcomes. The search for modifiable risk factors that can influence patient outcomes has led to increased interest in the role of micronutrients, such as vitamin D and magnesium, due to their immunomodulatory and anti-inflammatory properties.

Vitamin D is known for its classic role in calcium and bone metabolism; however, recent evidence highlights its broader biological functions, including regulation of the immune response, modulation of inflammation, and maintenance of the endothelial barrier. Low levels of vitamin D in intensive care patients cause many negative consequences, including infections (Amrein et al., 2014). Despite these associations, clinical trials and observational studies present mixed findings regarding the impact of vitamin D deficiency on sepsis outcomes, with some studies indicating a correlation with increased mortality, while others show no significant effect (Lan et al., 2020; Geiger et al., 2024).

Magnesium is another essential micronutrient with multiple roles in cellular metabolism, energy production, and as a co-factor for numerous enzymatic reactions. They also have important roles in conditions that have a function in the pathophysiology of sepsis, such as cytokine production, immune cell function and cardiac stability (Velissaris et al., 2015; Rosanoff et al., 2021). Hypomagnesemia has been linked to poor clinical outcomes in ICU patients, including prolonged hospital stays, increased severity scores, and higher mortality rates (Gonuguntla et al.,2023; Tonai et al., 2024). However, as with vitamin D, the evidence remains inconclusive regarding the direct impact of magnesium levels on sepsis prognosis. Understanding the interplay between micronutrient deficiencies and critical illness could have important implications for both the prevention and treatment of sepsis, potentially guiding personalized supplementation strategies to improve patient survival and recovery.

With this study, we aimed to evaluate the relationship of magnesium and vitamin D levels with septic shock and sepsis in patients admitted to the tertiary intensive care unit, and to evaluate the correlation of their deficiencies with the severity of the existing disease.

MATERIAL and METHOD

This retrospective study was conducted at the This retrospective study was conducted after obtaining approval from the Ataturk University Faculty of Medicine Local Ethics Committee. following the approval of the hospital's ethics committee (Ethics Committee Approval No: 39, Session No: 01, Date: February 13, 2019). Files and electronic records of 340 patients were examined. The study included a review of the medical records and electronic data of 299 patients diagnosed with sepsis or septic shock who were admitted to the Intensive Care Unit (ICU) of our Anesthesiology and Reanimation Department between January 1, 2017, and January 1, 2019. 41 patients were excluded from the study based on the exclusion criteria.

Patients were identified based on the Sepsis-3 diagnostic criteria outlined by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) (2016 guidelines) and subsequently confirmed for sepsis diagnosis through a reevaluation of these criteria using the recorded data. Patients who met the determined criteria were included in the study. Due to the lack of ScvO2 and cardiac index monitoring, these parameters were not used for diagnosis.

Inclusion and Exclusion Criteria

The inclusion criteria for the study were taken as: Admission to the intensive care clinic due to sepsis and/or septic shock, patients over 18 years of age, were not pregnant, had an ICU stay of more than 24 hours, did not have known renal insufficiency.

The exclusion criteria from the study were taken as: Did not have a diagnosis of sepsis or septic shock, were under the age of 18, were pregnant, stay in intensive care for less than 24 hours, had known chronic renal insufficiency, had incomplete medical records.

Data Collection

The following data were collected for the included patients: demographic characteristics, reasons for ICU admission, Glasgow Coma Scale (GCS) score on the day of admission, levels of procalcitonin (PCT), C-reactive protein (CRP), vitamin D, and magnesium (Mg), as well as the severity scores calculated within the first 24 hours of ICU admission, including the Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and Simplified Acute Physiology Score II (SAPS II). The same parameters (GCS, vitamin D level, Mg level, APACHE II, SOFA, and SAPS II scores) were recorded at the time of ICU discharge, along with the mortality and morbidity outcomes.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 22.0. The normality of data distribution was assessed using the Kolmogorov-Smirnov test and histograms. For normally distributed variables the Independent Sample t-test was employed, whereas non-normally distributed data were analyzed using the Mann-Whitney U test. The association between vitamin D and magnesium levels with mortality was evaluated using the chi-square test, while the Wilcoxon signed-rank test was used for score comparisons. Additionally, a correlation analysis was performed to assess the relationship between patient outcomes (discharge or death) and various clinical scores.

RESULTS

A total of 299 patients were hospitalized and treated in intensive care with septic shock and/or sepsis during the period covered by the study. The demographic and laboratory characteristics of these patients at the time of ICU admission are summarized in (Table 1). The mean age of the patients was 68.06 ± 17.17 years, with a nearly equal gender distribution (50.2% male, 49.8% female). The most common comorbid disease was respiratory failure. The mean Glasgow Coma Scale (GCS) score at admission was 8.17 ± 4.65.

A statistically significant difference was found between deceased and living patients in terms of average age, with non-survivors being older on average ($p = 0.017$). No statistically significant differences were noted in vitamin D levels or magnesium levels between survivors and non-survivors at admission and discharge when grouped by age (18-65 years and >65 years) (Table 2).

Patients with vitamin D levels <20 ng/mL did not show a significant difference in severity scores (GCS, APACHE II, SOFA, SAPS II) compared to those with levels >20 ng/mL. However, at ICU discharge, a higher proportion of patients with vitamin D levels <20 ng/mL was observed among non-survivors ($p < 0.001$). Magnesium levels were evaluated, revealing that patients with hypomagnesemia (<1.7 mEq/L) had significantly higher APACHE II and SOFA scores compared to those with normomagnesemia (>1.7 mEq/L), indicating worse clinical outcomes ($p < 0.05$) (Table3 and 4).

Table 1. Demographic and laboratory characteristics at the time of ICU admission

	All patients (n=299)
Age (years)	68.06±17.17
Gender (Male/Female) (%)	150(50.2) /149 (49.8)
Comorbidity (n)	
Respiratory Failure	215
Hypertension	137
Malignancy	85
Diabetes	73
Cerebrovascular Event	49
Cardiac Arrest	38
Other	124
GCS	8.17 ± 4.65
APACHE	25.93 ± 9.25
SOFA	8.59 ± 3.47
SAPSII	59.13 ± 19.06
CRP	113.07 ± 68.85
Procalcitonin	15.02 ± 33.31
Magnesium (mEq/L)	2.09 ± 1.33
D vit (ng/dL)	11.92 ± 14.16

Results were presented as mean ± standard deviation and as number.

Table 2. Comparison of Survivors and Non-Survivors by Age and Gender

	Survivors (n=86)		Non-Survivors (n=213)		P*
Age	63.86±18.72		69.27±16.93		0,017
Sex					
Female	46	(%53.5)	103	(%48.4)	0.422
Male	40	(%46.5)	110	(%51.6)	

Results were presented as mean ± standard deviation and as number. * $P > 0.05$

Analysis showed significant associations between clinical severity scores and patient outcomes. Higher APACHE II, SOFA, and SAPS II scores with increased mortality risk. Vitamin D levels were not significantly correlated with mortality, but lower levels were more frequent in non-survivors. Magnesium levels had a statistically significant association with mortality, particularly in older patients.

Table 3. Comparison of magnesium and vitamin D levels in patients aged 18-65 years and >65 years

		Survivor	Non-Survivor	p
Age 18-65	D vit (t1)	6.9 (0-98)	9.30 (0-92)	0,122
	D vit (t2)	9.95 (1.8-50)	9.2 (0.1-67)	0,709
	Magnesium (t1)	1.90 (1.10-4.60)	1.90 (0-4.10)	0,294
	magnesium (t2)	1.90 (1.10-3.50)	2.1(0.5-3.10)*	**0,016**
Age >65	Vitamin D (ng/dL) (t1)	7.70 (0.80-80)	7.2 (0-49)	0,641
	Vitamin D (ng/dL) (t2)	13.55 (1.1-82)**	9 (0-92)	**0,044**
	Magnesium (mEq/L) (t1)	1.95 (1.40-3.35)	2 (0.99-23)	0,693
	Magnesium (mEq/L) (t2)	1.80 (0.90-2.50)	1.9 (1-3.4)***	**0,016**

All data are presented as median (minimum-maximum). (t1: admission to ICU, t2: discharge)
* p <0.05 In favor of patients who died in the age group under 65
** P < 0.05 In favor of patients over the age of 65
*** p < 0.05 In favor of patients who died in the over 65 age group

Table 4. Scoring systems and biochemical markers according to magnesium levels.

	Hypomagnesemia (<1.7mEq/L) (n=91)	Normomagnesemia (>1.7 mEq/L) (n=208)	P
GKS	7.77±4.64 *	9.09±4.56	0.024
SOFA Score	9.00±3.58 *	7.68±3.07	0.003
APACHEII Score	27.23±9.50 *	22.97±7.94	<0.001
SAPS II	61.42±19.36 *	53.92±17.38	0.002
CRP	115.52±72.08	106.23±61.46	0.285
Procalcitonin	11.22±23.45	15.84±31.63	0.162

All data are presented as median (minimum-maximum)
* P < 0.05 The hospitalization was in favor of hypomagnesemia in terms of GKS, SOFA, APACHE 2, SAPS 2 scores.

DISCUSSION

In this study, vitamin D and magnesium levels and the correlation between the deficiency of these levels and the severity of the disease in patients admitted to the intensive care clinic with the diagnosis of septic shock and/or sepsis were evaluated.

Deficiency of vitamin D, which has an important role in the modulation of the immune system, has been associated with an increased tendency for infections in patients admitted to intensive care and an increase in 30-day mortality rates (Karampela et al., 2024; Wang et al., 2024). On the contrary, our findings revealed that while vitamin D deficiency was prevalent among these patients, its levels were not significantly associated with overall mortality. This observation is consistent with previous studies that reported similar results, where no definitive correlation was established between vitamin D levels and mortality in sepsis patients (Viglianti et al., 2019). In other words, it is not a risk factor for mortality (Aygencel et al., 2013).

Although vitamin D levels were found to be lower in patients over 65 years' old who succumbed during hospitalization, this difference was not statistically significant. This aligns with the literature, suggesting that while older patients are more prone to vitamin D deficiency, the direct impact of this deficiency on sepsis outcomes remains unclear. The fact that vitamin D supplementation did not substantially alter the outcomes further supports the hypothesis that low vitamin D levels might be a consequence rather than a cause of critical illness and sepsis.

Our analysis of magnesium levels indicated a significant association between hypomagnesemia and higher severity scores (GCS, SOFA, APACHE II, and SAPS II) at admission. Patients with low magnesium levels exhibited worse clinical markers, which suggests that magnesium might play a role in the pathophysiological response to sepsis. Previous studies have indicated that magnesium is involved in immune modulation and inflammatory responses, which are crucial in sepsis progression. However, despite its influence on severity scores, hypomagnesemia was not significantly linked to increased mortality in our study, mirroring the findings of other research in critical care settings.

Interestingly, our data showed that magnesium levels increased significantly from admission to discharge in non-survivors. This paradoxical increase in magnesium levels might reflect a compensatory response or a shift due to cellular damage in severe sepsis. This observation warrants further investigation, as the role of magnesium in sepsis remains complex and multifaceted. Our study also highlighted the limitations of using standard severity scores (GCS, SOFA, APACHE II, SAPS II) in predicting outcomes based solely on vitamin D and magnesium levels.

Despite the established role of these scoring systems in estimating patient prognosis, their predictive accuracy was not significantly enhanced by

incorporating vitamin D or magnesium levels, suggesting that other factors might play more critical roles in determining patient outcomes.

The role of magnesium in sepsis appears to be more pronounced. Our study demonstrated that hypomagnesemia was significantly associated with increased APACHE II, SOFA, and SAPS II scores, indicating a higher severity of illness in this group. These findings are supported by current literature (Limaye et al., 2011; Solanki et al., 2022; Laddhad et al., 2023), who reported that low magnesium levels were associated with increased duration of mechanical ventilation, increased days of intensive care unit stay, increased APACHE II scores, and increased mortality rates. Magnesium's crucial role in modulating inflammatory responses, stabilizing cellular membranes, and supporting energy metabolism makes it a vital element in managing critically ill patients, which might account for its stronger association with sepsis severity compared to vitamin D.

Interestingly, while Mg levels did not directly correlate with CRP or procalcitonin levels, its association with clinical severity scores points towards its role as a marker of overall physiological stress rather than a specific inflammatory marker. This observation aligns with the findings of Rubeiz et al. (Rubeiz et al., 1993), where Mg deficiency was linked to increased cytokine production and oxidative stress, further exacerbating multi-organ dysfunction in septic patients.

Our study has several limitations. Firstly, since our study was designed retrospectively, some data were found to be missing during the data review. Secondly, the levels of vitamin D and magnesium were adjusted according to our intensive care unit's routine treatment protocol, and no additional therapeutic modalities were applied to the patients. Thirdly, the impact of cytokines in sepsis on vitamin D and magnesium levels was not evaluated in our study. Due to the limited availability of cytokine levels measured periodically in the retrospective patient data, a complete data analysis could not be performed in these patients. Fourthly, the study was carried out in a third level intensive care clinic with a relatively small sample size of approximately 300 patients, which poses a limitation in terms of generalizability of the results. Lastly, the study group consisted entirely patients with sepsis, preventing a comparison of vitamin D and magnesium levels and mortality analysis in patients admitted to the tertiary intensive care clinic for reasons not related to sepsis.

In conclusion, while vitamin D and magnesium he levels in the patients we included in our study were not primarily associated with mortality rates, their roles in immune function and inflammation suggest they should not be overlooked in clinical practice. The observed trends indicate that these biomarkers may reflect underlying disease processes rather than act as independent prognostic factors. Further research is necessary to clarify their potential therapeutic implications in the management of sepsis.

Ethics Committee Approval

Ethical Issue: Ethical approval of the local ethics committee of Atatürk University Faculty of Medicine (Ethics Committee Approval No: 39, Session No: 01, Date: 13 February 2019).

Conflict of Interest

The authors declare that they have no conflict of interest regarding content of this article.

Financial Support

No financial support was received for this study. This study was supported by the author.

REFERENCES

Amrein K, Schnedl C, Holl A, Riedl R, Christopher KB, Pachler C, et al. (2014). Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. *Journal of the American Medical Association*, 312(15), 1520-1530.

Angus DC, van der Poll T. (2013). Severe sepsis and septic shock. *The New England Journal of Medicine*, 369(9) 840-851

Aygencel G, Turkoglu M, Tuncel AF, Candır BA, Bildacı YD, Pasaoglu H. (2013). Is Vitamin D insufficiency associated with mortality of critically ill patients? *Critical Care Research and Practice*, 856747.

Geiger C, McNally JD, Christopher KB, Amrein K. (2024). Vitamin D in the critically ill - update. *Current Opinion in Clinical Nutrition and Metabolic Care*, 27(6),515-522.

Gonuguntla V, Talwar V, Krishna B, Srinivasan G. (2023). Correlation of Serum Magnesium Levels with Clinical Outcome: A Prospective Observational Study in Critically Ill Patients Admitted to a Tertiary Care ICU in India. *Indian Journal of Critical Care Medicine*, 27(5),342-347.

Karampela I, Stratigou T, Antonakos G, Kounatidis D, Vallianou NG, Tsilingiris D, et al. (2024). 25-hydroxyvitamin D and parathyroid hormone in new onset sepsis: A prospective study in critically ill patients. *Metabolism Open*,100296.

Laddhad DS, Hingane V, Patil TR, Laddhad DD, Laddhad AD, Laddhad SD. (2023). An assessment of serum magnesium levels in critically ill patients: A prospective observational study. *International Journal of Critical Illness and Injury Science*, 13(3),111-117.

Lan SH, Lai CC, Chang SP, Lu LC, Hung SH, Lin WT. (2020). Vitamin D supplementation and the outcomes of critically ill adult patients: a systematic review and meta-analysis of randomized controlled trials. *Scientific Reports*, 10(1),14261.

Limaye CS, Londhey VA, Nadkart MY, Borges NE. (2011). Hypomagnesemia in critically ill

medical patients. *Journal of Association of Physicians of India*, 59:19-22.

Rhee C, Jones TM, Hamad Y, Pande A, Varon J, O'Brien C, et al. (2019). Prevalence, underlying causes, and preventability of sepsis-associated mortality in US Acute Care Hospitals. *JAMA Network Open*, 2(2), e187571.

Rosanoff A, Weaver CM, Rude RK. (2012). Suboptimal magnesium status in the United States: are the health consequences underestimated? *Nutrition Reviews*, 70(3),153-164.

Rubeiz GJ, Thill-Baharozian M, Hardie D, Carlson RW. (1993). Association of hypomagnesemia and mortality in acutely ill medical patients. *Critical Care Medicine*, 21(2), 203-209.

Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. (2020). Global, regional, and national sepsis incidence and mortality, 1990-2017: Analysis for the Global Burden of Disease Study. *Lancet*, 395(10219), 200-211.

Solanki J, Runwal K, Beke N, Bahulikar A, Phalgune D. (2022). Serum magnesium levels in critically Ill patients on admission in ICU and its correlation with outcome. *Journal of Association of Physicians of India*,70(5),11-12.

Tonai K, Katayama S, Koyama K, Imahase H, Nunomiya S. (2024). Association between hypomagnesemia and serum lactate levels in patients with sepsis: a retrospective observational study. *Journal of Anesthesia, Analgesia and Critical Care*, 3, 4(1), 23.

Velissaris D, Karamouzos V, Pierrakos C, Aretha D. Karanikolas M (2015). Hypomagnesemia in Critically Ill Sepsis Patients. *Journal of Clinical Medicine Research*, 7(12), 911-918.

Viglianti EM, Zajic P, Iwashyna TJ, Amrein K. (2019). Neither vitamin D levels nor supplementation are associated with the development of persistent critical illness: a retrospective cohort analysis. *Journal of Clinical Medicine Research*, 21(1), 39-44.

Wang AY, Yeh YC, Cheng KH, Han YY, Chiu CT, Chang CC, et al. (2024). Efficacy and safety of enteral supplementation with high-dose vitamin D in critically ill patients with vitamin D deficiency. *Journal of the Formosan Medical Association,* S0929-6646(24),241-249.

Yealy DM, Mohr NM, Shapiro NI, Venkatesh A, Jones AE, Self WH. (2021). Early care of adults with suspected sepsis in the emergency department and out-of-hospital environment: A consensus-based task force report. *Annals of Emergency Medicine*, 78(1), 1-19