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# Hypomagnesemia as a Predictor of Early Liver Dysfunction in Critically Ill Patients with Sepsis

## Sepsisli Kritik Hastalarda Erken Karaciğer Disfonksiyonunun Bir Göstergesi Olarak Hipomagnezemi

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**ABSTRACT**

**Aim:** Liver dysfunction is an early finding caused by the inflammation and hypoperfusion developed in sepsis. Magnesium deficiency may contribute to an excessive response to immune stress and inflammatory tissue damage in sepsis. This study aimed to evaluate the relationship between serum magnesium levels and early liver dysfunction (ELD) in patients with sepsis.
**Material and Methods:** 142 patients who developed sepsis were divided into two groups according to their liver function, as sequential organ failure assessment (SOFA) hepatic subscore <2 (Non-ELD, n=72) and SOFA hepatic subscore ≥2 (ELD, n=70). The disease severity, including the acute physiology and chronic health evaluation (APACHE) II score and the SOFA score, biochemical determination, and microbiological cultures were evaluated.
**Results:** ELD patients presented APACHE II and total SOFA scores higher than Non-ELD patients, while $PaO_2/FiO_2$ ratios were significantly lower (both p<0.001). Hypomagnesemia and hypoalbuminemia were independently associated with ELD (OR: 6.55, 95% CI: 2.62-16.36, and OR: 4.62, 95% CI: 1.35-15.84, respectively). To predict ELD, the area under the curve was 0.81 (95% CI: 0.74-0.89, p<0.001) and 0.70 (95% CI, 0.61-0.79; p<0.001) for serum magnesium and albumin, respectively. The mortality rate in all septic patients was 35.0% for hypomagnesemia and 25.6% for normomagnesemia (p=0.065). The mortality rate in ELD patients was 34.1% for hypomagnesemia and 30.7% for normomagnesemia (p=0.415).
**Conclusion:** The reduction of magnesium levels was associated with increased rates of ELD in critically ill patients with sepsis. Admission hypomagnesemia did not adversely affect mortality neither in all sepsis patients nor in those who developed ELD.
**Keywords:** Critically ill; hypomagnesemia; liver; mortality; sepsis.

**ÖZ**

**Amaç:** Karaciğer disfonksiyonu, sepsiste gelişen inflamasyon ve hipoperfüzyonun neden olduğu erken bir bulgudur. Magnezyum eksikliği, immün strese karşı aşırı bir yanıta ve sepsiste inflamatuar doku hasarına katkıda bulunabilir. Bu çalışmada, sepsisli hastalarda serum magnezyum düzeyleri ile erken karaciğer disfonksiyonu (early liver dysfunction, ELD) arasındaki ilişkinin değerlendirilmesi amaçlandı.
**Gereç ve Yöntemler:** Sepsis gelişen 142 hasta karaciğer fonksiyonlarına göre ardışık organ yetmezliği değerlendirme (sequential organ failure assessment, SOFA) karaciğer alt skoru <2 olanlar (Non-ELD, n=72) ve SOFA karaciğer alt skoru ≥2 olanlar (ELD, n=70) olmak üzere iki gruba ayrıldı. Akut fizyoloji ve kronik sağlık değerlendirmesi (acute physiology and chronic health evaluation, APACHE) II skoru ve SOFA skoru dahil olmak üzere hastalık şiddeti, biyokimyasal belirleme ve mikrobiyolojik kültürler değerlendirildi.
**Bulgular:** ELD hastalarının APACHE II ve toplam SOFA skorları ELD olmayan hastalara göre daha yüksek iken, $PaO_2/FiO_2$ oranları anlamlı derecede düşüktü (her ikisi için p<0,001). Hipomagnezemi ve hipoalbüminemi ELD ile bağımsız şekilde ilişkiliydi (sırasıyla, OR: 6,55; %95 GA: 2,62-16,36 ve OR: 4,62; %95 GA: 1,35-15,84). ELD'yi öngörmede, serum magnezyum ve albümini için eğri altındaki alan sırasıyla 0,81 (%95 GA: 0,74-0,89; p<0,001) ve 0,70 (%95 GA: 0,61-0,79; p<0,001) idi. Tüm septik hastalardaki ölüm oranı, hipomagnezemi için %35,0 ve normomagnezemi için %25,6 idi (p=0,065). ELD hastalarındaki ölüm oranı hipomagnezemi için %34,1 ve normomagnezemi için %30,7 idi (p=0,415).
**Sonuç:** Magnezyum düzeylerindeki azalma, sepsisli kritik hastalarda artmış ELD oranları ile ilişkiliydi. Kabuldeki hipomagnezemi ne tüm sepsisli hastalarda, ne de ELD gelişenlerde mortaliteyi olumsuz etkilemedi.
**Anahtar kelimeler:** Kritik hasta; hipomagnezemi; karaciğer; mortalite; sepsis.

## INTRODUCTION

Sepsis is known as life-threatening organ dysfunction resulting from an uncontrolled host response to infection (1). In addition to playing an important role in the defense against microorganisms, the liver is also frequently exposed to dysregulated inflammation (2). The development of liver dysfunction and failure, which is a serious complication due to the ongoing inflammation and hypoperfusion in sepsis, directly promotes the severity of the disease and death (3). Mortality rates in sepsis patients with liver dysfunction or failure are between 54% and 68%, and these mortality rates are higher than the dysfunction or failure of the lung, which is the most commonly affected organ in sepsis (4).

The incidence of hypomagnesemia in critically ill patients reaches up to 65%. The predisposition of critically ill patients to symptomatic or asymptomatic magnesium deficiency may lead to important clinical conditions such as hypokalemia, hypocalcemia, cardiac arrhythmias, neurotoxicity, sepsis, and psychiatric problems, resulting in increased morbidity and mortality (5,6).

In experimental models, magnesium deficiency causes inflammation, and latent magnesium deficiency is associated with chronic low-grade inflammation (7). Moreover, magnesium deficiency shows pro-oxidant effects by increasing lipid peroxidation in liver mitochondria (8). Dietary magnesium intake is inversely related to serum C-reactive protein (CRP) levels (9), and magnesium supplementation reduces CRP levels in individuals with inflammation (10).

It has been shown that treatments aimed at reducing the inflammation process can alleviate sepsis-induced liver injury (11). Magnesium supplementation inhibits the upregulation of inflammatory molecules in cells treated with endotoxin (12) and also provides significant protection against lipopolysaccharide (LPS) induced liver injury (13). To date, evidence that low magnesium levels may facilitate sepsis-induced liver dysfunction has lacked. On this basis, we conducted this study with the hypothesis that a subclinical magnesium deficiency exacerbates sepsis-induced inflammation and could be associated with early liver dysfunction (ELD) in critically ill patients suffering from sepsis.

## MATERIAL AND METHODS

### Study Design

In this cohort study of prospective character, adult patients (age of ≥18 years) admitted consecutively to a 42-bed department of the medical-surgical intensive care unit (ICU) of Konya Numune Hospital diagnosed with sepsis during a 16-month period from March 2021 to July 2022 were included. It was made in accordance with the Declaration of Helsinki and approved by the ethics committee of Necmettin Erbakan University (approval date/no: 2021/3083). The patients participating in the study or their relatives provided written informed consent.

### Inclusion and Exclusion Criteria

Inclusion criteria were the recent onset of sepsis and/or septic shock (at diagnosis or within the first 24 h) according to the SEPSIS-3 definition (1). Exclusion criteria were documented hypomagnesemia or magnesium supplementation prior to the diagnosis of sepsis, hypermagnesemia, preexisting liver disease, hemolytic disease, bilirubin ≥2 mg/dL in the previous 30 days, previous immunodeficiency, history of daily cortisol medication >5 mg, blood product transfusion, malignant disease of any origin, seizures, and pregnancy.

### Definitions

The ELD was defined as serum bilirubin ≥2 mg/dL (a SOFA hepatic subscore ≥2) within 48 hours after the onset of sepsis (14). The normal range for magnesium concentration in our laboratory was 1.80-2.60 mg/dL. A magnesium level in serum of <1.80 mg/dL was considered hypomagnesemia, and ≥2.61 mg/dL hypermagnesemia. Magnesium-lowering drugs included mannitol, diuretics, aminoglycosides, amphotericin B, proton pump inhibitors, and digoxin. The requirement for mechanical ventilation was recorded if initiated within the first 48 hours after admission. The main site of causative infection was determined by microbiological results or clinical suspicions and signs of infection.

For the outcomes, death from any cause occurring within 30 days after the onset of sepsis was defined as 30-day mortality. Sepsis-related mortality was considered when the patient died without definitive infection control.

### Study Protocol

One hundred and forty-two patients who developed sepsis were divided into two groups according to their liver functions: sequential organ failure assessment (SOFA) hepatic subscore <2 (Non-ELD, n=72) and SOFA hepatic subscore ≥2 (ELD, n=70). The disease severity assessment, including the acute physiology and chronic health evaluation (APACHE) II score and the SOFA score, biochemical determination, and microbiological cultures were evaluated within 24 hours after ICU admission and before the initiation of antimicrobial therapy against sepsis. Serum magnesium levels were measured with the original reagents using AU5800 biochemical analyzer (Beckman Coulter, California, USA). The levels of the other parameters were measured according to routine laboratory working procedures at the local institute. In this study, no interference was made in the routine treatment process in the ICU and appropriate magnesium replacement was given to all patients in the ELD and Non-ELD groups with low magnesium levels (n=44, and n=16, respectively). Additionally, only admission magnesium levels were examined in detail and post-replacement magnesium values were not evaluated. Routine sepsis therapy (fluids, antibiotics, catecholamines, surgery) according to the current sepsis guidelines was administered to all the patients (15). The primary endpoints of this study were the relation between serum magnesium levels and the occurrence of ELD in critically ill patients affected by sepsis. The secondary outcome measures were the impact of low magnesium levels on all-cause ICU mortality within 30 days.

### Sample Size

The G*Power v.3.1 software was used for the sample size calculation. This analysis was performed according to the results of a similar study by Vatsalya et al. (16). In order to detect a significant difference in magnesium level among the two groups, a power analysis was carried out using a 2-sided independent samples t-test with a confidence level of 95% ($p<0.050$), an effect size of 49%,

and a power of 80%. Considering a 5% dropout rate, the sample size was finally calculated as at least 141 patients.

**Statistical Analysis**

For the statistical analysis, IBM SPSS v.21.0 and MedCalc v.14.12 software were used. Mean±standard deviation or median, interquartile range, min-max were chosen to express continuous variables and numbers and percentages for categorical data. The distribution of the continuous variables was evaluated by the Kolmogorov-Smirnov test. For comparing continuous variables between patients with and without ELD, for normally distributed data, the independent samples t-test was used, and for non-normal data, the Mann-Whitney U test. Categorical variables were compared with the Chi-square test or Fisher's exact test. A logistic regression model was used to examine the ionic factors associated with the development of ELD. Based on the results of the multivariate analysis, the predictive capacity of serum magnesium and albumin levels in the differentiation of ELD was evaluated by the receiver operating characteristic (ROC) curve analysis. The correlations were evaluated using Spearman's correlation test. The Cox regression analysis and the Kaplan-Meier method were performed for time-to-event analyses. A p value of lower than 0.050 was defined as statistically significant.

## RESULTS

In the study period, 191 critically ill and with new-onset sepsis patients were enrolled. The leading criteria for exclusion were preexisting liver disease or hyperbilirubinemia (n=16), immunodeficiency or cortisol medication (n=15), hypermagnesemia (n=13), and preexisting hypomagnesemia or magnesium supplementation (n=5). Finally, 142 intensive care patients were incorporated into the study for analysis. The baseline traits of patients at admission were shown in Table 1. The most common systemic disease in septic patients was cardiovascular disease, with 27%. ELD patients had higher APACHE II and total SOFA scores than Non-ELD patients, while the $PaO_2/FiO_2$ ratios were significantly lower (both $p<0.001$). The mortality rates were higher in ELD patients, but this difference was not statistically significant. No statistically significant difference was observed between ELD and Non-ELD patients in terms of other variables.

When the laboratory parameters were evaluated, ELD patients had higher CRP, procalcitonin (PCT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, international normalized ratio (INR), lactate, and lactate/albumin levels, while hemoglobin, magnesium, and albumin levels were lower than Non-ELD patients (Table 2). The microbiological profile was similar in both groups (Table 3).

The risk of ELD associated with ionic disturbance was analyzed using logistic regression. After adjustment according to age, gender, and APACHE II scores, the multivariate regression analysis describing hypomagnesemia and hypoalbuminemia as independently associated with ELD (Odds ratio, (OR): 6.55, 95% CI: 2.62-16.36, p=0.001, and OR: 4.62, 95% CI: 1.35-15.84, p=0.015, respectively) showed the important effect of the decrease

**Table 1.** Baseline characteristics of patients

| | Non-ELD (n=72) | ELD (n=70) | p | Total (n=142) |
|---|---|---|---|---|
| **Age** (year), median (IQR) [min-max] | 66 (60-74) [17-87] | 70 (61-78) [21-82] | 0.066 | 67.5 (60-76) [17-87] |
| **Gender**, (male), n (%) | 40 (55.6) | 38 (54.3) | 0.879 | 78 (54.9) |
| **Cause of ICU admission**, n (%) | | | | |
| Medical | 59 (81.9) | 52 (74.3) | 0.269 | 111 (78.2) |
| Trauma/Surgery | 13 (18.1) | 18 (25.7) | | 31 (21.8) |
| **APACHE II score**, mean±SD | 23.2±3.2 | 25.2±3.3 | **<0.001** | 24.2±3.4 |
| **SOFA score**, median (IQR) [min-max] | 6 (5-8) [4-11] | 8 (7-9) [4-12] | **<0.001** | 7 (5-9) [4-12] |
| **Diabetes mellitus**, n (%) | 13 (18.1) | 15 (21.4) | 0.614 | 28 (19.7) |
| **Cardiovascular disease**, n (%) | 20 (27.8) | 18 (25.7) | 0.781 | 38 (26.8) |
| **Neurologic disease**, n (%) | 12 (16.7) | 10 (14.3) | 0.695 | 22 (15.5) |
| **Pulmonary disease**, n (%) | 13 (18.1) | 16 (22.9) | 0.478 | 29 (20.4) |
| **Renal disease**, n (%) | 14 (19.4) | 12 (17.1) | 0.723 | 26 (18.3) |
| **At least one co-morbid illness**, n (%) | 47 (65.3) | 48 (68.6) | 0.677 | 95 (66.9) |
| **Body temperature** (°C), mean±SD | 37.8±1.0 | 37.5±0.9 | 0.069 | 37.7±1.0 |
| **MAP** (mmHg), mean±SD | 75.1±12.7 | 71.5±11.4 | 0.084 | 73.3±12.1 |
| **Heart rate** (bpm) | 89 (67-116) [49-150] | 95 (63-125) [51-152] | 0.710 | 91 (66-120) [49-152] |
| **Respiratory rate** (bpm) | 18 (15-24) [12-35] | 21 (17-26) [13-37] | 0.057 | 20 (16-25) [12-37] |
| **Worst $PaO_2/FiO_2$ at admission** | 301 (295-331) [282-380] | 284 (280-298) [275-351] | **<0.001** | 295 (284-312) [275-380] |
| **Antibiotic exposure**, n (%) | 50 (69.4) | 52 (74.3) | 0.521 | 102 (71.8) |
| **Magnesium lowering drugs**, n (%) | 51 (70.8) | 54 (77.1) | 0.392 | 105 (73.9) |
| **Total parenteral nutrition**, n (%) | 8 (11.1) | 11 (15.7) | 0.421 | 19 (13.4) |
| **Mechanical ventilation**, n (%) | 21 (29.2) | 24 (34.3) | 0.512 | 45 (31.7) |
| **Septic shock**, n (%) | 20 (27.8) | 27 (38.6) | 0.172 | 47 (33.1) |
| **Time from sepsis to death** (days) | 10 (6-14) [3-28] | 9 (6-13) [4-29] | 0.844 | 9.5 (6-13) [3-29] |
| **ICU length of stay** (days) | 17 (10-27) [3-37] | 14.5 (7-23) [3-38] | 0.121 | 16 (8-25) [3-38] |
| **Sepsis-related mortality**, n (%) | 14 (19.4) | 17 (24.3) | 0.485 | 31 (21.8) |
| **30-day mortality**, n (%) | 19 (26.4) | 23 (32.9) | 0.398 | 42 (29.6) |

ELD: early liver dysfunction, ICU: intensive care unit, APACHE: acute physiological and chronic health evaluation, SOFA: sequential organ failure assessment, MAP: mean arterial pressure, $PaO_2/FiO_2$: ratio of arterial oxygen concentration to the fraction of inspired oxygen, IQR: interquartile range ($25^{th}$-$75^{th}$ percentile), SD: standard deviation

**Table 2.** Laboratory parameters according to liver dysfunction

| | Non-ELD (n=72) | ELD (n=70) | p | Normal Values |
|---|---|---|---|---|
| **White blood cell count** ($mm^3$) | 14.8±5.7 | 16.0±5.2 | 0.190 | 3.91-10.9 |
| **Hemoglobin** (g/dL) | 12.4±2.7 | 11.1±2.4 | **0.003** | 13.5-16.9 |
| **Platelet count** ($10^9$/L) | 132 (104-266) [85-479] | 125 (95-269) [81-466] | 0.225 | 166-308 |
| **Erythrocyte sedimentation rate** (mm/h) | 93.5 (56-106) [16-144] | 89.5 (52-106) [14-121] | 0.329 | 0-20 |
| **C-reactive protein** (mg/dL) | 143.0±33.6 | 167.9±36.6 | **<0.001** | 0-8 |
| **Procalcitonin** (ng/mL) | 17.4 (9-23) [0.1-49.0] | 24.3 (19-30) [0.1-39.0] | **0.002** | 0-0.5 |
| **Aspartate aminotransferase** (IU/L) | 38 (28-57) [10-267] | 50 (32-64) [15-273] | **0.043** | 3-50 |
| **Alanine aminotransferase** (IU/L) | 36.5 (27-55) [9-259] | 40 (31-63) [16-266] | 0.177 | 3-50 |
| **Alkaline phosphatase** (IU/L) | 109.4 (84-124) [30-200] | 121 (86-167) [32-211] | **0.032** | 30-120 |
| **Blood urea nitrogen** (mg/dL) | 31.9 (26-42) [19-114] | 38.9 (28-49) [12-110] | 0.083 | 17-43 |
| **Creatinine** (mg/dL) | 1.2 (1.0-1.5) [0.5-2.6] | 1.5 (0.9-2.2) [0.4-2.9] | 0.294 | 0.67-1.17 |
| **Bilirubin** (mg/dL) | 1.6 (1.3-1.8) [0.6-1.9] | 2.6 (2.3-2.8) [2.0-5.5] | **<0.001** | 0-1.2 |
| **International normalized ratio** | 1.4±0.4 | 1.5±0.3 | **0.043** | 0.8-1.2 |
| **Sodium** (mmol/L) | 139.1±10.9 | 137.2±11.3 | 0.305 | 136-145 |
| **Potassium** (mmol/L) | 4.0±0.9 | 4.2±0.9 | 0.276 | 3.5-5.1 |
| **Calcium** (mg/dL) | 8.6 (8.1-9.3) [6.9-11.0] | 8.4 (7.3-9.4) [6.8-10.4] | 0.073 | 8.8-10.6 |
| **Ionized $Ca^{2+}$** (mmol/L) | 1.2 (1.1-1.3) [1.0-1.4] | 1.2 (1.1-1.2) [1.0-1.5] | 0.112 | 1.15-1.33 |
| **Magnesium** (mg/dL) | 2.1 (1.9-2.4) [1.5-2.6] | 1.6 (1.5-1.8) [1.5-2.5] | **<0.001** | 1.8-2.6 |
| **Phosphate** (mg/dL) | 3.7±0.7 | 3.9±0.8 | 0.090 | 2.5-4.5 |
| **Chlorine** (mmol/L) | 103 (100-109) [90-122] | 105 (101-118) [93-131] | 0.077 | 101-109 |
| **Lactate** (mmol/L) | 2.2±0.8 | 2.7±0.9 | **<0.001** | 0-2 |
| **Albumin** (g/dL) | 3 (2.7-3.6) [2.5-5.0] | 2.7 (2.5-3.1) [2.4-4.6] | **<0.001** | 3.5-5.2 |
| **Lactate/Albumin ratio** | 0.7 (0.5-0.9) [0.2-1.4] | 1.0 (0.7-1.3) [0.3-1.5] | **<0.001** | |

ELD: early liver dysfunction, descriptive statistics were shown as mean±standard deviation or median (interquartile ranges, $25^{th}$-$75^{th}$ percentile) [minimum-maximum]

in magnesium levels on the development of liver dysfunction in septic patients (Figure 1). As these serum biomarkers have been demonstrated to be significantly associated with liver dysfunction in septic patients, the levels of magnesium and albumin were evaluated by ROC analysis as predictive indicators of ELD. The area under the curve (AUC) was 0.81 (95% CI: 0.74-0.89, p<0.001) and 0.70 (95% CI: 0.61-0.79, p<0.001) for serum magnesium and albumin, respectively. The sensitivities of magnesium and albumin were 80% and 50%, while the specificity was 77.8% and 87.5%, respectively (Figure 2). The pairwise comparison of ROC curves for predicting liver dysfunction showed significant differences in the AUC values of magnesium and albumin (difference between areas: 0.11, SE: 0.05, 95% CI: 0.02-0.21, z=2.31; p=0.020). Therefore, serum magnesium may have a higher predictive value than serum albumin in the evaluation of developing liver dysfunction in septic patients.

The relationship between the SOFA score, by which the organ dysfunction was evaluated, and magnesium was measured by bivariate analysis. Although there was no significant correlation between the SOFA score and magnesium in the Non-ELD group (r=-0.214, p=0.074), there was a weak inverse correlation between the SOFA score and magnesium in the ELD group (r=-0.252, p=0.032).

**Table 3.** Comparison of microbiological profile between patients with and without early liver dysfunction

| | Non-ELD (n=72) | ELD (n=70) | p |
|---|---|---|---|
| **Microbiologically documented infection**, n (%) | 53 (73.6) | 49 (70.0) | 0.632 |
| **Blood culture positive**, n (%) | 28 (38.9) | 24 (34.3) | 0.569 |
| **Source of Infection** | **Non-ELD (n=53)** | **ELD (n=49)** | **p** |
| **Respiratory**, n (%) | 21 (39.6) | 18 (36.7) | 0.764 |
| **Urinary tract**, n (%) | 12 (22.6) | 11 (22.4) | 0.981 |
| **Skin/soft tissues**, n (%) | 5 (9.4) | 6 (12.2) | 0.647 |
| **Intraabdominal**, n (%) | 4 (7.5) | 6 (12.2) | 0.515 |
| **Other**, n (%) | 11 (20.8) | 8 (16.3) | 0.566 |
| **Identified Microorganisms** | **Non-ELD (n=53)** | **ELD (n=49)** | **p** |
| **Gram-negative**, n (%) | 20 (37.7) | 21 (42.9) | 0.598 |
| **Gram-positive**, n (%) | 15 (28.3) | 12 (24.5) | 0.663 |
| **Polymicrobial**, n (%) | 6 (11.3) | 9 (18.4) | 0.315 |
| **Atypical**, n (%) | 2 (3.8) | 1 (2.0) | 1.000 |
| **Fungal**, n (%) | 4 (7.5) | 3 (6.1) | 1.000 |
| **Viral**, n (%) | 6 (11.3) | 3 (6.1) | 0.491 |

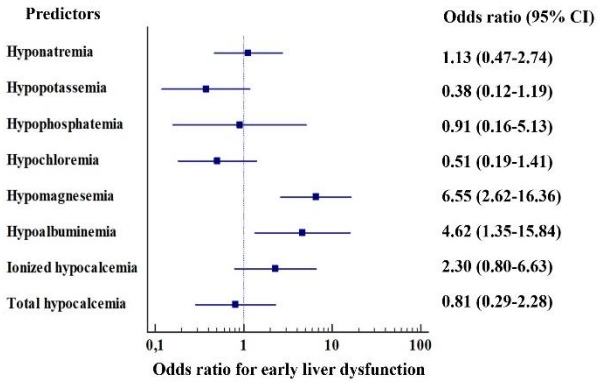


**Figure 1.** Ionic factors were possibly associated with ELD. All ionic parameter covariate calculations were adjusted for age, sex, and APACHE II score.

The comparison of the effect of liver dysfunction on the mortality of septic patients was shown in Table 1. Although the sepsis-related and 30-day mortality rates were higher in patients in the ELD group than in the Non-ELD group, this difference was insignificant (p=0.485, p=0.398, respectively). We performed an interaction analysis to determine whether ELD carries a high risk of mortality in patients with sepsis and whether this risk is associated with the inflammatory and pro-oxidant function of low magnesium levels. We tested the interaction between bilirubin below or above 2 mg/dL and magnesium levels for 30-day mortality. But no interaction was found (p=0.654). Also, in the Cox regression analysis of septic patients without liver dysfunction, low magnesium levels were not associated with ICU mortality (p=0.183).

To further investigate the impact of hypomagnesemia on the clinical outcome of septic patients, we performed a time-dependent mortality analysis. The Kaplan-Meier curves for normomagnesemic and hypomagnesemic patients were shown in Figure 3. The mortality rate for all septic patients was 25.6% for normomagnesemia vs 35.0% for hypomagnesemia (p=0.065, log-rank test). The mortality rate in ELD patients was 30.7% for normomagnesemia vs 34.1% for hypomagnesemia (p=0.415, log-rank test). Finally, the risk of mortality associated with hypomagnesemia remained unchanged in both septic patients and those who developed liver dysfunction, as it was shown by the survival curve analysis.

## DISCUSSION

In this study, the relationship between low magnesium levels in sepsis patients with the development of ELD and its effects on ICU mortality were investigated. Low magnesium levels in critically ill septic patients were associated with increased liver dysfunction. The hypomagnesemia at admission had no effect either on mortality in all the sepsis patients or in those who developed ELD.

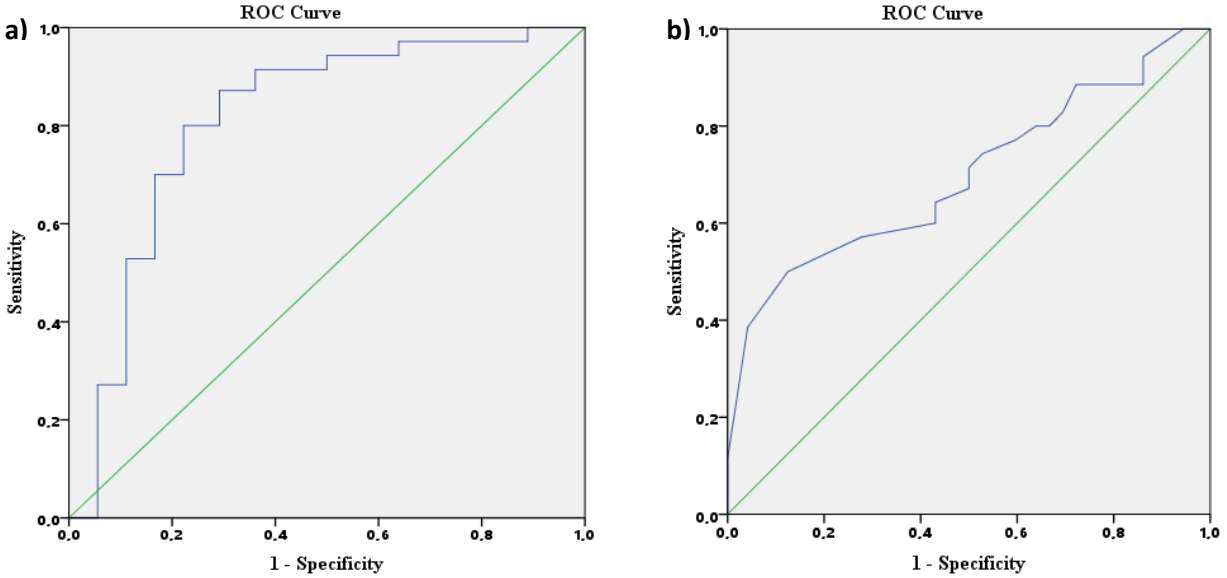


**Figure 2.** Receiver operating characteristic curves for **a)** magnesium and **b)** albumin to predict early liver dysfunction

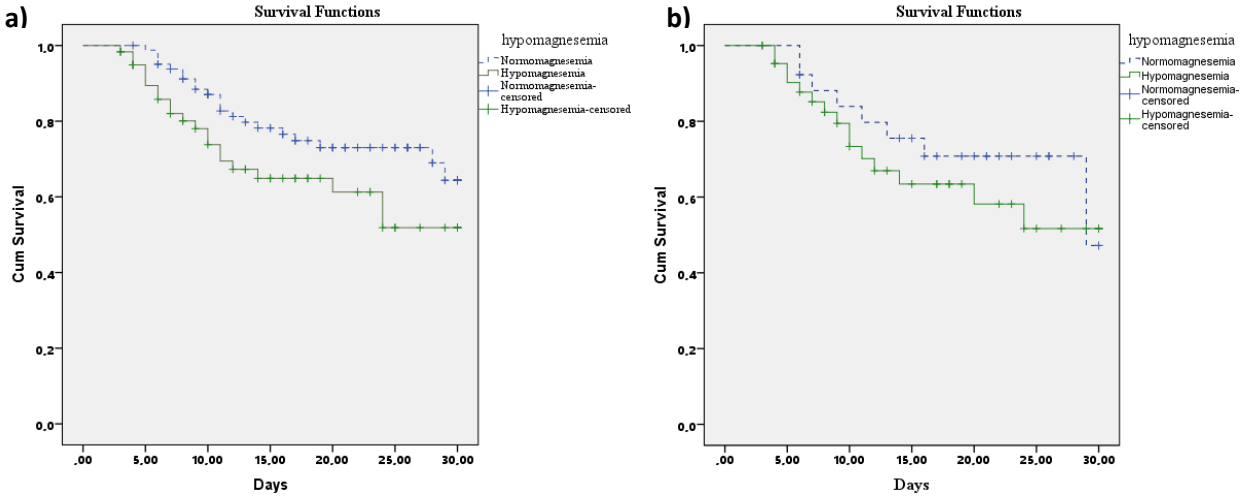


**Figure 3.** The survival after the onset of sepsis in patients with normomagnesemia and hypomagnesemia was estimated using the Kaplan-Meier method. **a)** Probability of survival in all septic patients with normomagnesemia (n=82; 21 death) and hypomagnesemia (n=60; 21 death) (p=0.065, log-rank test). **b)** Probability of survival in ELD patients with normomagnesemia (n=26; 8 death) and hypomagnesemia (n=44; 15 death) (p=0.415, log-rank test)

The mediators released by the innate immune cells in sepsis and their effects on endothelial cells lead to endothelial leakage, extravascular migration of neutrophils and inflammatory mediators, vasodilation, and coagulation activation, resulting in organ dysfunctions (17). Factors such as steatosis, cholestasis, hepatocellular injury, hepatic mitochondrial respiration, and the disruption of cellular regeneration play a role in clinical septic hepatic dysfunction (18). Despite the increase in cardiac output and hepatic perfusion, hepatocellular function has been shown to decrease in the early period after the onset of sepsis (19). Inflammatory jaundice may occur due to direct bacterial products or due to the response of the host to infection. Cholestatic liver dysfunction is, through hepatocellular and ductular cholestasis mechanisms, directly related to the immunological processes occurring during sepsis and systemic inflammation in the liver (20). Sepsis jaundice, which is usually cholestatic, may emerge before other clinical signs of the underlying infection are seen, with mild increases in serum alkaline phosphatase and aminotransferases (21). Although there are no standard diagnostic criteria and terminology, the limited increases in alkaline phosphatase and liver enzymes, along with the mild deviation in coagulation accompanying the increase in total bilirubin in our study, is consistent with the cholestatic form of sepsis-associated liver dysfunction (22).

The incidence of electrolyte disturbances, sepsis, and septic shock is increased in patients with hypomagnesemia (23). Magnesium modulates the immune response, including macrophage activation, lymphocyte proliferation, and increased production of reactive oxygen species, and magnesium deficiency might increase the production of inflammatory cytokines (24). In the experimental endotoxemia study of Lee et al. (25), magnesium sulfate was shown to dose-dependently reduce the inflammatory response, oxidative stress, and acute injury in the lung.

However, there have not been enough clinical studies on the role of magnesium in the liver. Hernandez et al. (26) studied the effects of magnesium supplementation on hepatic inflammation in non-hypertensive obese women. It showed that oral magnesium supplementation decreased serum ALT levels in hypomagnesemic obese women. In another randomized study, Karandish et al. (27) investigated the effect on liver enzymes of magnesium supplementation in patients with nonalcoholic fatty liver disease. Unlike the previous study, it was reported that magnesium supplementation did not affect liver enzymes. However, this study was conducted in normomagnesemic patients and used lower doses of magnesium.

In an experimental endotoxic model, Sayeed et al. (28) showed that the hepatic $Mg^{2+}$ content of septic rats was significantly lower than non-septic controls. Gunther et al. (8) suggested that the non-Hb Fe increase induced by the magnesium deficiency in the liver cell fractions may play a role in the increase of lipid peroxidation in liver mitochondria. Calviello et al. (29) found that in magnesium deficiency, liver glutathione, CuZn-superoxide dismutase, and vitamin E decreased, while lipid peroxidation increased in liver microsomes, and this was associated with oxidative stress. George et al. (30) showed that a primary disorder in the energy metabolism of the liver mitochondria is produced in magnesium deficiency and that, secondary, protein synthesis is inhibited. In our study, it was found that hypomagnesemia is related to an increased incidence of ELD in septic patients. Consistent with previous studies, these findings might explain the higher incidence of liver dysfunction in patients with hypomagnesemia.

Hypomagnesemia may cause inflammatory tissue damage by increasing acute phase proteins, cytokine biosynthesis, and the production of reactive oxygen species (7,24). Since the severity of the disease in septic patients can be considered a direct indicator of multiple organ dysfunction in response to excessive systemic inflammation (31), in our study, the significant correlations between the SOFA score and magnesium levels in patients in the ELD group suggested that our results are consistent with findings proving the correlation between increased inflammatory response and serum magnesium. Theoretically, the severity of the organ dysfunction assessed by the SOFA score is, as in other inflammatory conditions, an important indicator of acute phase changes in the inflammatory mediators of septic patients. Therefore, inverse correlations between magnesium and the SOFA score can be expected, similar to the inverse relationships between acute phase reactants and cytokines and magnesium.

In liver dysfunction, subtle changes are observed in the hepatocellular functions due to the clearance functions or the decreased synthesis (4). In the absence of underlying liver disease, the correlation between mild to moderate liver dysfunction to mortality is not clear enough. Kramer et al. (14) showed that liver dysfunction is an early sign of sepsis and that ELD is associated with a bad prognosis in septic critically ill patients. In a recent multi-center study, Jensen et al. (32) evaluated the prognostic impact on critically ill patients with mild to moderate liver impairment. It was found that sepsis-related acute liver impairment was seen in the early period of ICU admission and was associated with high mortality. However, liver impairment had no effect on mortality in patients without severe infection. Nesseler et al. (33) evaluated the association of liver dysfunction with long-term mortality in patients with septic shock. Although during the septic shock, there was a significant correlation between new-onset or worsening liver dysfunction and mortality up to 6 months, the same correlation was not observed for baseline liver dysfunction on days 28, 90, and 180. In the present study, the fact that liver dysfunction does not contribute to an increase in the risk of death in patients with sepsis suggests that ELD may be an indicator of more severe disease but is not associated with increased mortality.

Several possibilities can explain the divergent results in the studies evaluating the effects of septic liver dysfunction on mortality. First, the studies have been conducted at a high rate in patients with sepsis without signs of shock, different definitions for liver injury have been used, and short-term mortality has been evaluated (34). Second, patients with more severe liver dysfunction were included in the evaluation due to the restrictive definitions of liver dysfunction (35). The increase in serum bilirubin and alkaline phosphatase are early signs of hepatic dysfunction in patients with sepsis (4). However, although the increase of liver enzymes (aspartate and alanine aminotransferase) is associated with liver injury, it is not an indicator of a decrease in the active hepatocellular function that precedes

hepatocyte injury (36). Despite the fact that bilirubin does not have enough specificity as the only indicator of liver dysfunction, the broader definition of liver dysfunction as SOFA hepatic subscore ≥2 in our study enabled the inclusion of those with subtle septic liver injury and to evaluate the possible major effects of a low-grade injury. Third, ELD lacking symptoms in routine clinical parameters during sepsis is more common (37). Fourth, although the increased bilirubin levels-defining liver dysfunction is an independent predictor of mortality (15,32), there may be a significant time delay between liver damage and the development of hyperbilirubinemia (20).

The studies evaluating the relationship between hypomagnesemia and mortality provided differing results. In the study of Chen et al. (6) in which the 1st-day magnesium levels of critically ill patients were evaluated, when compared to normomagnesemic patients, no difference in age, gender, APACHE II scores, and other electrolyte levels was observed in the hypomagnesemic patients. However, hypomagnesemia was associated with an increased risk of mortality. In the study of Soliman et al. (38), in which the levels of ionized magnesium of critically ill patients were evaluated, although admission hypomagnesemia was not associated with clinical outcomes, ionized hypomagnesemia developing during ICU stay was associated with poor prognosis. This was explained by the strong correlation between ionized hypomagnesemia and sepsis and septic shock. In the study of Chernow et al. (39), in which they evaluated the relationship between magnesium levels and clinical outcomes in postoperative intensive care patients, mortality in patients with admission hypomagnesemia was similar to that in patients with normomagnesemia. However, the increase in mortality was evident in patients with severe hypomagnesemia. Kvarantan et al. (40) studied patients with severe hypomagnesemia upon admission to the ICU. It was shown that although the incidence of hypomagnesemia is high in ICU patients, severe hypomagnesemia is unusual and, unlike the literature, not associated with mortality. In our study, similarly to previous results, admission hypomagnesemia had no effect on the mortality of critically ill septic patients. This may be related to the mild hypomagnesemia of our patients and the administration of magnesium replacement therapy in the intensive care unit.

This study had some limitations. First, disease severity showed baseline differences between the study groups. Although we tried to control for this by covariate inclusion of APACHE II scores in the regression analysis, unmeasurable differences between groups may not have been accounted for. This might lead to variation in the magnitude of the effects observed. Second, we sampled serum magnesium levels only at admission to the ICU. Therefore, the concentrations of magnesium and their effects on septic liver dysfunction could not be evaluated during the course of the disease. Third, septic patients with hypermagnesemia were excluded from the study in line with the procedure in similar studies (23). Although hypermagnesemia occurred in only 13 of the otherwise available 191 patients, this may cause selection bias. Fourth, the assessment of magnesium status in critically ill patients was limited to serum levels. Since magnesium deficiency may occur even when magnesium levels are normal (24), misclassifying patients with hypomagnesemia may lead to bias. However, in this study, the fact that the mild to moderate hypomagnesemia present in hypomagnesemic patients was mostly associated with a true magnesium deficiency. Finally, although a risk factor that may cause confusion was excluded by the nonadmission of patients with preexisting liver disease, the deterioration in liver function, which we identified with static tests in ICU admission, may be caused by different motives, including undiagnosed liver disease. Despite these limitations, our results suggest that hypomagnesemia in septic patients might be an independent liver dysfunction risk factor. Further randomized controlled trials are needed to determine whether magnesium supplementation for the correction or prevention of hypomagnesemia reduces the development of ELD by attenuating sepsis-induced inflammation with potential immunomodulatory effects.

## CONCLUSION

Hypomagnesemia was found to be associated with an increased risk of developing liver dysfunction in critically ill patients with sepsis. Admission hypomagnesemia was in association with mortality neither in all septic patients nor in those who developed ELD.

**Ethics Committee Approval:** The study was approved by the Non-Interventional Clinical Research Ethics Committee of Necmettin Erbakan University (05.02.2021, 3083).

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