

## ADMISSION HYPOMAGNESEMIA

### - Impact on Mortality or Morbidity in critically ill patients -

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#### Abstract

**Background/Objective:** No previous study exists to evaluate admission serum magnesium level as a predictor of morbidity or mortality. The aim of this study was to define the prevalence of admission hypomagnesemia in critically ill patients and to evaluate its relationship with organ dysfunction, length of stay, and mortality.

**Methods:** A retrospective study was done on 100 patients  $\geq 16$  years old, admitted to the medical-surgical intensive care unit (ICU) at the University Hospital over 2 years period. Observations were made on admission total serum magnesium level, a variety of lab tests related to magnesium, need for ventilator, duration of mechanical ventilation, hospital/ICU lengths of stay, and general patient demographics.

**Results:** The serum magnesium level (normal value, 1.3-2.1 mEq/L) was measured at admission. At admission, 51% of patients had hypomagnesemia, 49% had normal magnesium levels. There was significant difference in mortality rate (55% vs 35%), the length of hospital ( $15.29 \pm 0.66$  vs  $12.81 \pm 0.91$ ), or ICU ( $9.16 \pm 0.53$  vs  $5.71 \pm 0.55$ ) stay between these two groups of patients ( $p < 0.05$  for all). Hypomagnesemic patients more frequently had total hypocalcemia, hypokalemia, and hyponatremia. A total of 51 patients developed hypomagnesemia during

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their ICU stay; these patients had higher Acute Physiology And Chronic Health Evaluation II (APACHE II) ( $14.16 \pm 1.03$  vs  $10.80 \pm 0.94$ ) and Sequential Organ Failure Assessment (SOFA;  $10.89 \pm 0.90$  vs  $7.58 \pm 5.01$ ) scores at admission ( $p < 0.01$  for both), a higher maximum SOFA score during their ICU stay ( $14.75 \pm 0.73$  vs  $8.08 \pm 0.52$ ,  $p < 0.01$ ), a more need to ventilator (58.6% vs 41.4%,  $p < 0.05$ ), and longer duration of mechanical ventilation (7.2 vs 4.7 day,  $p < 0.01$ ) than the other patients. The ROC curve of SOFA score in the hypomagnesemia yields significantly better results than APACHE II. An increase of 5 units in the APACHE II or SOFA measured on admission increase relative probability of hypomagnesemia by a factor of 0.12 and 0.16 respectively.

**Conclusion:** Development of hypomagnesemia during an ICU stay is associated with guarded prognosis. Monitoring of serum magnesium levels may have prognostic, and perhaps therapeutic, implications.

**Key words:** magnesium; critical care; Sequential Organ Failure Assessment score; electrolytes; mechanical ventilation; mortality.

## Introduction

Magnesium is the fourth most abundant cation in the human body and the second most abundant intracellular cation after potassium. Magnesium (Mg) is pivotal in the transfer, storage, and utilization of energy as it regulates and catalyzes >300 enzyme systems<sup>1,2</sup>.

Magnesium deficiency has been associated with a number of clinical manifestations such as atrial and ventricular arrhythmias, cardiac insufficiency, coronary spasm, sudden death, skeletal and respiratory muscle weakness, bronchospasm, tetany, seizures, and other neuromuscular abnormalities and a number of electrolyte abnormalities, including hypokalemia, hypocalcemia, hyponatremia, and hypophosphatemia<sup>1,3-6</sup>.

Hypomagnesemia is one of the most common electrolyte disturbances in hospitalized patients, especially in the critically ill. The Prevalence of hypomagnesemia (measuring total serum magnesium) has a wide range (11% to 61%), and considerable controversy exists regarding

its effects on morbidity and mortality<sup>7-9</sup>.

Various changes in Mg can occur during the perioperative period. Plasma concentrations are decreased after abdominal<sup>10</sup>, heart<sup>11</sup>, or orthopedic surgery<sup>12</sup>. This disorder is often overlooked, although it should probably be searched for systematically because of its significance for the prognosis of patients<sup>13</sup>.

The severity of hypomagnesemia can be assessed using subjective clinical evaluation and biochemical markers of organ dysfunction. Objective scoring systems such as, the Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores, are also commonly used to assess severity of illness and to predict outcome in other groups of critically ill patients<sup>14,15</sup>. The scoring systems may identify high-risk groups among the critically ill, to whom therapeutic interventions may be directed in order to reduce morbidity and mortality, and comparisons may be made of the benefit of such interventions<sup>15</sup>.

In the general population with hypomagnesemia, the predictive abilities of APACHE II and SOFA have not been evaluated. The APACHE II score incorporates 12 physiologic variables, age, and an assessment of chronic diseases in individual patients<sup>14</sup>. The SOFA score was developed through a consensus process<sup>16</sup> and afterwards validated in a larger population of 1449 critically ill patients<sup>17</sup>. SOFA is composed of scores from six organ systems (respiratory, cardiovascular, hepatic, coagulation, renal, and neurological) graded from 0 to 4 according to the degree of dysfunction/failure<sup>17</sup>. There is a paucity of data evaluating serum magnesium at admission as a predictor of morbidity or mortality.

The aim of this study was to define the prevalence of admission hypomagnesemia in critically ill patients and to evaluate the relationship of magnesium level to organ failure, length of stay, electrolyte disturbance, ventilator need, duration of mechanical ventilation, and mortality rate. Also, this study was undertaken to establish the value of the APACHE II and SOFA scores in determining the patient's morbidity and mortality in the critically ill hypomagnesemic patients admitted to an intensive care unit (ICU).

## Materials and Methods

A single center, retrospective trial. was done on 100 patients  $\geq 16$  years old who were admitted for 3 or more days to the adult medical-surgical ICU at the Alzahra Hospital in Esfahan, Iran from April 1, 2004 through December 31, 2005. The study was approved by the University and Hospital Ethics Committees.

Survey was conducted on admission total serum magnesium level, the variety of lab tests related to magnesium, ventilator need, duration of mechanical ventilation, hospital/ICU lengths of stay, and general patient demographics.

Patient charts were analyzed to allow classification into categories, depending on the precipitating factors leading to hypomagnesemia. Those with burn injury, renal failure, Mg administration, and addiction were excluded from data collection.

Heart rate and arrhythmias at admission and during hospital stay were recorded. Tachycardia was defined as a heart rate of  $>90$  beats/min, and myocardial ischemia as a depression of ST segment of  $\geq 1$  mm on the electrocardiogram.

Renal dysfunction was defined by a serum creatinine of  $>1.2$  mg/dL.

The Acute Physiology And Chronic Health Evaluation (APACHE) II score<sup>14</sup> was determined on the first day. The Sequential Organ Failure Assessment (SOFA) score<sup>17</sup> was determined at the day of admission and every day until discharge. The worst values for each day were recorded. The maximum SOFA score was also recorded during the ICU stay. Total serum magnesium (Mg) concentrations were recorded at the day of admission to the ICU.

Other routine laboratory investigations included (normal values): sodium (136-142 mEq/L), potassium (3.8-5 mEq/L), total serum calcium (8.2-10.6 mg/dL), phosphate (2.5-4.5 mg/dL), total bilirubin ( $<1.2$  mg/dL), creatinine (0.4-1.3 mg/dL), and glucose (70-110 mg/dL). Patients were considered hyperglycemic with an admission glucose concentration  $>11$  mmol/l ( $>200$  mg/dL) on hospital days 1 or 2.

Duration of ventilation was defined as the number of days with

mechanical ventilation. Patients were classified into two groups according to their initial Mg level: hypomagnesemia (<1.3 mEq/L) and normomagnesemia (1.3-2.1 mEq/L).

Data was analysed using the statistical program SPSS for window, Release 11. All values are reported as mean  $\pm$  SE. Chisquare and Fisher's exact tests were used for categorical variables. Multiple logistic regression analysis was performed to determine the independent risk factors for developing hypomagnesemia during the ICU stay. Relative risk is given with the 95% confidence interval (CI). Pearson's correlation coefficient and linear regression were used to evaluate the relationship between Mg and other variables. A *p* value of <0.05 was considered as statistically significant.

## Results

Of the total of 115 patients, 15 patients were excluded because of inability to obtain the Mg measurement at admission. Of the 100 patients studied, 62 (62%) were surgical (Table 1).

*Table 1*  
*Clinical diagnosis of patients*

<b>Diagnosis</b>	<b>n</b>
Surgical	
Gastrointestinal surgery	38
Thoracic surgery	11
Trauma	8
Others	5
Total	62
Medical	
Cerebrovascular accident	2
Drug intoxication	4
Pulmonary thromboembolism	7
Sepsis	9
Respiratory failure	6
Myasthenia gravis	2
Cirrhosis	1
Others	7
Total	38

At admission, 51 patients (51%) had hypomagnesemia, 49 (49%) had normomagnesemia (Table 2).

Table 2  
Demographic data, disease severity, and outcome according to Mg at admission (mean  $\pm$  SE).

	Low Mg	Normal Mg
No. of patients (%)	51 (51)	49 (49)
Mg concentration (mEq/L)	1.08 $\pm$ 0.02*	1.98 $\pm$ 0.06
Age, yrs	60.27 $\pm$ 0.82	58.84 $\pm$ 0.86
Weight, Kg	62.80 $\pm$ 1.90	65.94 $\pm$ 2.53
Gender (%)		
Male	26 (51)	21 (43)
Female	25 (49)	28 (57)
APACHE II score	14.16 $\pm$ 1.03*	10.80 $\pm$ 0.94
Sofa admission score	10.89 $\pm$ 0.90*	7.58 $\pm$ 5.01
Maximum sofa score	14.75 $\pm$ 0.73§	8.08 $\pm$ 0.52
ICU stay, day	9.16 $\pm$ 0.53§	5.71 $\pm$ 0.55
Hospital stay, day	15.29 $\pm$ 0.66§	12.81 $\pm$ 0.91
Mortality, n (%)	28 (55)*	16 (33)
Need ventilator, n (%)	41 (58.6)*	29 (41.4)
Duration of MV, day	7.2 (0.65)*	4.7 (0.62)

APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment.

ICU: Intensive Care Unit, Mg: Magnesium.

\*  $p < 0.05$  hypomagnesemia vs normomagnesemia.

§  $p < 0.01$  hypomagnesemia vs normomagnesemia.

MV: mechanical ventilation.

There was significant difference in the prevalence of hypomagnesemia among surgical and medical patients. In the surgical patients, hypomagnesemia was most common after gastrointestinal surgery (64%), and in the medical patients, was most common in severe sepsis and septic shock (48%). (Table 1) There was no difference in age, sex, and weight at admission between groups. The hypomagnesemic group had a greater total SOFA score and APACHE II score at admission than the normomagnesemic group (Table 2). There was significant difference in ICU and hospital length of stay or mortality among groups.

Patients in hypomagnesemic group had significantly more need to ventilatory support than normomagnesemic patients. Duration of mechanical ventilation was significantly more in patients with low serum Mg compared with normomagnesemic patients (Table 2). Hypomagnesemic patients had a higher maximum SOFA score during their ICU stay than normomagnesemic patients (Table 2). By univariate logistic regression, hypomagnesemia at admission was an independent risk factor for mortality (odds ratio, 2.51; 95% CI, 1.11-5.66;  $p = 0.024$ ).

The hypomagnesemic patients had a faster heart rate and more arrhythmias than normomagnesemic patients. Past medical history revealed that hypomagnesemic patients suffered significantly more of hypertension, diabetes mellitus, as well as hyponatremia, hypokalemia, and hypocalcemia. Hypophosphatemia was slightly more common in hypomagnesemic group (not significant) (Table 3).

*Table 3*  
*Incidence of arrhythmias, hypertension, diabetes, electrolyte disturbance, and ventilator need among the two groups at admission.*

	Low Mg n (%)	Normal Mg n (%)
Heart rate, beats/min	78.24 ± 1.12*	67.35 ± 0.78
Arrhythmia	18 (81.8)*	4 (18.8)
Past history		
Hypertension	30 (68.2)*	14 (31.8)
Diabetes Mellitus	11 (84.6)*	2 (15.4)
Electrolyte disturbance		
Hyponatremia	23 (67.6)*	11 (32.4)
Hypokalemia	22 (84.6)*	4 (15.4)
Hypocalcemia	23 (67.6)*	11 (32.4)
Hypophosphatemia	20 (51.3)	19 (48.7)

\*  $p < 0.05$  hypomagnesemia vs normomagnesemia.

In all patients, there was a weak direct relationship between magnesium concentrations and hypokalemia ( $r^2 = 0.205$ ,  $p = 0.04$ ), hypocalcemia ( $r^2 = 0.366$ ,  $p = 0.00$ ). There was inverse relation between Mg concentration and suctioning of nasogastric tube ( $r^2 = -0.255$ ,  $p =$

0.01), history of hypertension ( $r^2 = -0.313$ ,  $p = 0.002$ ), history of diabetes mellitus ( $r^2 = -0.202$ ,  $p = 0.04$ ), arrhythmia ( $r^2 = -0.261$ ,  $p = 0.009$ ), ICU stay ( $r^2 = -0.492$ ,  $p = 0.00$ ), hospital stay ( $r^2 = -0.293$ ,  $p = 0.003$ ), APACHE II score ( $r^2 = -0.368$ ,  $p = 0.00$ ), Sofa score ( $r^2 = -0.351$ ,  $p = 0.00$ ), and duration of MV ( $r^2 = -0.224$ ,  $p = 0.029$ ).

Compared with normomagnesemic patients, hypomagnesemic patients had greater risk of developing hypokalemia (odds ratio, 1.65; 95% CI, 1.25-2.08;  $p < 0.05$ ), hypocalcemia (odds ratio, 1.413; 95% CI, 1.06-1.88;  $p < 0.05$ ), arrhythmia (odds ratio, 1.419; 95% CI, 1.14-1.77;  $p < 0.05$ ), and hyponatremia (odds ratio, 1.301; 95% CI, 1.01-1.67;  $p < 0.05$ ).

Hypomagnesemia did not significantly increase risk of need for ventilator or mortality.

Independent risk factors for development of hypomagnesemia during the ICU stay were the type of nutrition (odds ratio, 1.11; CI, 1.01-1.21;  $P < 0.05$ ), gastric drainage (odds ratio, 1.56; CI, 1.19-2.52;  $P < 0.05$ ), past medical history of hypertension (odds ratio, 1.74; CI, 1.20-2.52;  $p < 0.05$ ) or diabetes mellitus (odds ratio, 1.22; CI, 1.05-1.43;  $p < 0.05$ ).

Hypomagnesemia did not significantly increase risk of need ventilator or mortality. No relation was found between Mg and phosphate.

The sensitivity, specificity, Youden index, and area of the Receiver Operating Characteristic (ROC) curve at the best cutoff point for hypomagnesemia are presented in Table 4. There are no statistical differences in Youden index and area under the ROC curve among APACHE II and SOFA.

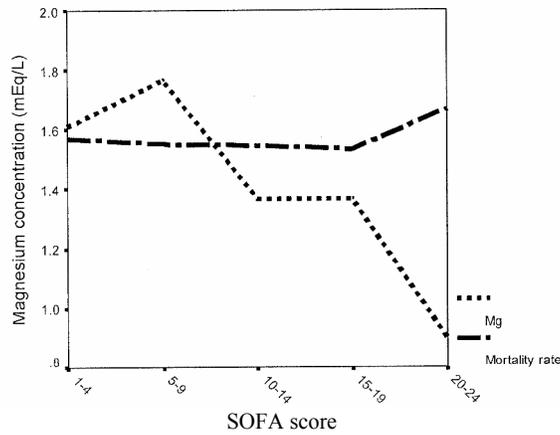
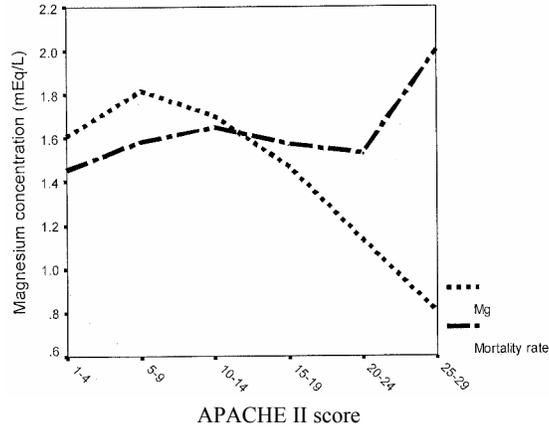
Table 4  
Comparison of the assessment scores in hypomagnesemia

	Cut-off point	Sensitivity (%)	Specificity (%)	Youden index	ROC area
APACHE II	15	75.0	57.6	0.33	0.59 ± 0.05
SOFA score	8	87.5	52.3	0.50	0.67 ± 0.07

APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment Score; ROC: Receiver Operating Characteristic.

The distribution of scores on day 1 and probability of hospital mortality derived from each scoring system and magnesium concentration are shown in Fig. 1.

*Fig. 1*  
*Distribution of the Acute Physiology and Chronic Health Evaluation (APACHE II) scores, the Sequential Organ Failure Assessment Score (SOFA), magnesium concentration, and hospital mortality rate in the study patients in each category. The higher the scores in APACHE II or SOFA and the lowest magnesium concentration, the higher the mortality. Mg, magnesium concentration.*

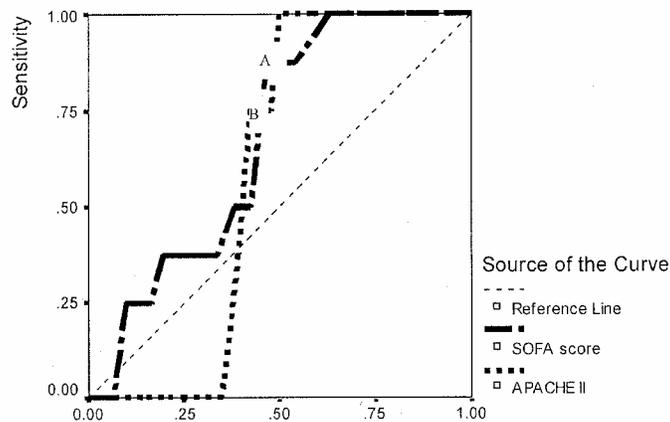


The ROC curve for hypomagnesemia is shown in Fig. 2. All two scoring systems provide good discrimination in ROC curves. The ROC curve of SOFA score in the hypomagnesemia yields significantly better results than APACHE II. Therefore, the SOFA score itself plays a crucial role in the prediction of hypomagnesemia.

An increase of 5 units in the APACHE II or SOFA measured on admission increase relative probability of hypomagnesemia by a factor of 0.12 and 0.16 respectively. A decrease of 1 mEq/L in serum magnesium concentration increased the relative probability of need ventilator or time ventilated by a factor of 0.77 and 0.38 respectively.

Fig. 2

Receiver Operating Characteristic (ROC) curves drawn at different cut-off values for Acute Physiology and chronic Health Evaluation (APACHE II) and Sequential Organ Failure Assessment Score (SOFA). The area under the curve of SOFA-ROC is larger but there is no statistical difference when compared with APACHE II. The dotted diagonal line indicates no discrimination. The best cut-off point in ROC of the two score systems is marked "A" (score = 8) for SOFA, "B" (score = 15) for APACHE II.



## Discussion

In mammals, the magnesium ion plays an important role at the intracellular level as free magnesium regulates intermediary metabolism,

DNA and RNA synthesis and structure, cell growth, reproduction and membrane structure, transport of potassium and calcium ions, signal transduction modulation, and fat and protein synthesis. Magnesium is a cofactor for most adenosine triphosphates because it is the adenosine triphosphate – magnesium complex that is bound and hydrolyzed by enzymes<sup>1-3</sup>.

The prevalence of hypomagnesemia in critically ill adult patients varies between 14-66%<sup>7-9,18</sup>.

The relation between hypomagnesemia and mortality has varied among studies. Rubeiz et al<sup>19</sup> reported nearly double the mortality rates (46% vs 25%) in hypomagnesemic patients compared with those with normomagnesemia. Guerin et al.<sup>9</sup> found no difference in ICU mortality between hypomagnesemic and normomagnesemic patients (18% vs 17%). Chernow et al.<sup>8</sup> similarly reported no difference in mortality between hypomagnesemic and normomagnesemic patients (13% vs 11%). Our results showed significant difference in ICU mortality between patients with hypomagnesemia or normomagnesemia at admission.

Hypomagnesemia has long been known to be associated with diabetes mellitus and insulin resistance. Magnesium supplementation is associated with decreased insulin requirements and better control of blood sugar<sup>20</sup>. In our series, patients with history of diabetes or higher blood glucose at admission had more incidence of hypomagnesemia, suggesting that diabetes represents one factor among many.

Although hypomagnesemia has been associated with hypertension<sup>21</sup>, contrary to our study, this association was very poor.

Magnesium depletion has been implicated in cardiac arrhythmias, especially when accompanied by hypokalemia, or in patients with poor left-ventricular function. The antiarrhythmic properties of magnesium administration have been well established<sup>22</sup>. In our study, more patients had tachycardia in the hypomagnesemic group at admission, and there was significant difference in the prevalence of arrhythmias.

Hypomagnesemia is commonly associated with other electrolyte disturbances<sup>5,23,24</sup>. Whang et al.<sup>5</sup> found hypomagnesemia in 42% of

patients with hypokalemia, 29% of patients with hypophosphatemia, 27% of patients with hyponatremia, and 22% of patients with hypocalcemia. Hypokalemia is commonly observed in hypomagnesemic patients and is relatively refractory to isolated potassium supplementation until magnesium deficiency is corrected. This relation can be due to underlying disorders that cause both magnesium and potassium loss, such as diuretic therapy, vomiting, and diarrhea. In addition, renal potassium losses are increased in hypomagnesemic patients<sup>5,24</sup>. We found a greater prevalence of hypokalemia or hyponatremia in hypomagnesemic than in normomagnesemic patients.

Hypocalcemia is also frequently found in association with magnesium depletion<sup>25</sup>. The mechanism is multifactorial and involves defects in the release and synthesis of parathyroid hormone and resistance to parathyroid hormone<sup>23</sup>. We also found an increased prevalence of total hypocalcemia in hypomagnesemic than in normomagnesemic patients.

Hypomagnesemic patients had more severe organ dysfunction and higher APACHE II core than the other patients. This may be explained by a strong association of hypomagnesemia with sepsis and septic shock, a common cause of death in the ICU patient.

The prevalence of hypomagnesemia was particularly common in patients with sepsis and septic shock. Sepsis was one of the independent risk factors for developing hypomagnesemia during the ICU stay. Magnesium may play an important role in sepsis, as magnesium ions are essential for several important immunologic functions and serve as a natural calcium antagonist, an important step in propagating cellular injury<sup>26</sup>. In animal models, magnesium deficiency increased production of inflammatory cytokines with increases in lethality associated with endotoxin challenge<sup>27</sup>. Salem et al.<sup>28</sup> showed that progressive magnesium deficiency and hypomagnesemia are strongly associated with increased mortality in experimental sepsis, and magnesium replacement therapy provides significant protection from an endotoxin challenge. Harkema and Chaudry<sup>29</sup> reviewed studies involving the administration of adenosine triphosphate – magnesium chloride. These authors found that adenosine

triphosphate – magnesium chloride, given to restore cellular bioenergetics, improved organ function and survival time in a variety of animal models of oligemic shock, ischemia, and sepsis and in human volunteers and patients with shock.

Comparison of the APACHE II and SOFA score, reveals that the accuracy of the APACHE II is not significantly better than that of the SOFA for hypomagnesemia. The APACHE II is not much better than SOFA score in the prediction of hypomagnesemia, because many biases are found in the use of the APACHE system: First, treatment error is not predictable, especially in surgical patients<sup>30</sup>. Second, the data collected on the day of admission may not reflect completely the unforeseen events which restore them to their previous health and quality of life. The latter is more meaningful, because the functional results are as important as the mortality prediction<sup>31</sup>. The appropriate allocation of limited resources available should be considered when decisions are made.

Although SOFA score yielded a sensitivity of up to 87.5%, far better than that of APACHE II (75%) for prediction of hypomagnesemia, this still does not justify its application to individual patients for prediction of low Mg. Decision-making however, in terms of transferring patients from ICU, the reinforcement of medical treatment or surgical intervention, may be changed if we make sequential records of the scoring system for individual patients.

The admission SOFA reflects the degree of failure already present when the patient enters the ICU. This measurement, the only admission mortality prediction model<sup>32</sup>, is able to achieve, can be used to stratify patients according to severity of illness, for example, inclusion in clinical trials based on the admission SOFA score.

In conclusion, the development of hypomagnesemia during the ICU stay is associated with higher morbidity and mortality rates that may be the result of prolonged disease, administration of diuretics, or sepsis. The SOFA score predicts hypomagnesemia better than APACHE II. Whether ionized hypomagnesemia directly contributes to cellular alterations or is only a marker of critical illness cannot be determined from the present data. A prospective study is indicated to verify observations regarding

outcome prediction, to identify appropriate interventions in the high-risk patient, to confirm the potential benefit of magnesium supplementation to prevent or correct hypomagnesemia in critically ill patients, and to determine the impact, if any, of other organ system dysfunction.

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