A Study of Utility of Serum Magnesium Level as a Prognostic Marker in Critically Ill Patients

Manoj Gupta¹, Nipun Agrawal², Tariq Mahmood³, Lalit Singh⁴

¹Associate Professor, Department of Biochemistry, Sri Ram murti Smarak Institute of Medical Sciences, Bareilly, UP, India.
²Associate Professor, Department of Community Medicine, Sri Ram murti Smarak Institute of Medical Sciences, Bareilly, UP, India.
³Professor and HOD, Department of Biochemistry, Sri Ram murti Smarak Institute of Medical Sciences, Bareilly, UP, India.
⁴Professor and HOD, Department of Respiratory Medicine and Critical Care Medicine, Sri Ram murti Smarak Institute of Medical Sciences, Bareilly, UP, India.

Abstract

Background: Prognostication has an important role in patient care. It allows for us to define patients at higher risk of adverse outcome. It also helps us to judiciously manage resources for the best possible outcome of such patients. It is an ongoing task to find new, simpler and more accurate prognostic markers. Magnesium is a very important mineral in our physiology. It is a co enzyme of at least 300 enzymes specially kinases. Hypomagnesemia has often been reported in critically ill patients but measurement of serum magnesium level among the critically ill is still not a standardized practice.

Material and Methods: This is an observational cohort study comprising of 150 patients admitted to the Medical Intensive care unit (MICU) of a tertiary care super specialty hospital between September 2018 to February 2020, between the age groups of 15 to 100 years of age. Only patients who were admitted to the MICU ward were included in the study. Patients with multi organ dysfunction were included in the study. Patients of polytrauma were excluded from the study. Patients who took discharge against medical advice were dropped from the study. Any patient who did not give consent to treatment or for mechanical ventilation was excluded from the study.

Results: 111 (74%) subjects were suffering from hypomagnesemia. 38 (25.33%) were normomagnesemic and only one subject had hypermagnesemia. The difference in the serum magnesium levels between the normomagnesemic and hypomagnesemic subjects was statistically significant. There was an inverse and significant correlation between the APACHE II score and serum magnesium levels (r= -0.211 p = 0.01). There was an inverse and significant correlation between the serum magnesium levels and the numbers of days of MICU stay (r= -0.318 p= 0.000). There was also an inverse and significant correlation between the serum magnesium levels and the numbers of days of mechanical ventilation required by a patient (r= -0.303 and a p= 0.001).

Conclusion: Serum magnesium levels are an important marker in predicting prognosis of a critically ill patient. Serum magnesium levels can be used to predict mortality and morbidity in critically ill patients and can also be used to predict extended stay in ICU, requirement of ventilation and extended period of ventilation in such patients.

Keywords: Serum Magnesium level.

Introduction

Prognostication has an important role in patient care. It prevents discordant expectation in regards to patient outcome between attendants and doctors. It allows for us to define patients...
at higher risk of adverse outcome. It also helps us to judiciously manage resources for the best possible outcome of such patients. A number of different models have been proposed for prognostication of critically ill patients such as acute physiology and chronic health evaluation (APACHE), simplified acute physiology score (SAPS) and mortality prediction model (MPM) etc.\textsuperscript{[1,2]} But it is an ongoing task to find new, simpler and more accurate prognostic markers.\textsuperscript{[3,4]}

Magnesium is often referred to as the ‘Fifth forgotten ion’. It is because, in spite of various studies attesting to its importance specially in critically ill patients, its abnormality is still massively underdiagnosed in hospitalized patients.\textsuperscript{[5,6]}

Magnesium is a co enzyme for more than 300 enzymes. Magnesium acts as co enzyme for all kinases including the ubiquitous protein kinases, all enzymes with ATPase activity, all enzymes acting on nucleotides etc. It is essential for energy metabolism, regulation of cellular pathways, synthesis of DNA and RNA. Mg\textsuperscript{++} is essential to cellular function and life itself because of the large number of reactions it is involved in.\textsuperscript{[7]} Hence deficiency of magnesium can have a deleterious effect on the cellular metabolism and cause cellular dysfunction which is an important cause of morbidity and mortality in critically ill patients.\textsuperscript{[8]}

Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score was introduced as method of predicting risk of mortality in critically ill patients in 1985.\textsuperscript{[9]} It generates a point score ranging from 0 to 71 based on 12 physiologic variables, age, and underlying health conditions. These variables are chosen as they represent a wide spectrum of organ function, are reliable and objective and are routinely measured. These 12 variables include vitals such as heart rate, mean blood pressure, respiratory rate, temperature, Glasgow Coma Score, and hematological and biochemical parameters such as hematocrit, white blood cell count, serum potassium, serum sodium, serum creatinine, serum pH and PaO\textsubscript{2}. Systemic illnesses such as cardiovascular disorders, hepatic disorders, Pulmonary and renal insufficiencies and immunocompromised states are also considered in the APACHE II scoring system.\textsuperscript{[10]}

One variable conspicuous by its absence in the APACHE II scoring system is serum Magnesium level.

Our study intended to evaluate serum magnesium levels as a predictor of morbidity and mortality among critically ill patients.

**Material and Methods**

The study was conducted as an observational cohort study. The cohort comprised of 150 critically ill patients admitted to the Medical Intensive care unit (MICU) of a tertiary care super specialty hospital of Rohilkhand region, between September 2018 to February 2020, of the age groups of 15 to 100 years of age.

Critically ill patients admitted to the MICU ward were included in the study. Patients with multi organ dysfunction were included in the study.

Patients of polytrauma were excluded from the study. Patients who took discharge against medical advice were dropped from the study. Any patient who did not give consent to treatment or for mechanical ventilation was excluded from the study. Patients who had history of post hospitalization magnesium supplementation were also excluded from the study.

A detailed history of the patient was obtained from the patient or his/her attendants. All vitals were recorded at the time of admission. Hematological and biochemical routine investigations were sent on the day of admission. Serum Magnesium levels were measured on the day of admission.

All biochemical parameters were analyzed in the routine biochemistry laboratory of the hospital and all hematological parameters were measured in the hematology laboratory of the
Serum pH and PaO2 were measured by point of care testing at the MICU. All diagnostic labs used were validated by means of internal quality control as well as external quality validation. APACHE II scoring was done using an online APACHE II score calculator of Clincalc.com (https://clincalc.com/IcuMortality/APACHEII.aspx). The progression of the patient was recorded. Notes were made in regards to requirement of mechanical ventilation in the patient and if so for what duration. Both serum magnesium levels as well as APACHE II score were studied for their value in prognostication of morbidity and mortality in critically ill patients. Statistical analysis was done by means of Excel 2011 and SPSS 26.

**Results**

A total of 150 patients were chosen to be part of the cohort. Of them 44 (29.33%) were female and 106 (70.67%) were male. Youngest patient was 17 years old and oldest patient was 92 years old. Median age of patients was 60 years. Of the 150 patients enrolled in the study 79 (52%) were shifted out of the MICU to ward and 71 (48%) expired in the MICU.

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<th>Table 1: Demographics and group distribution of subjects</th>
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<tr>
<td><strong>Total Subjects (n)</strong></td>
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The average age of the patients who were shifted out of the MICU to ward for further recovery was 56.15 (±10.29 years). The average age of the patients who expired in the MICU was 64.24 (±11.24) years. This age difference was statistically significant with a p value of <0.0001. The average serum magnesium level of the study cohort was 1.56 (± 0.32) mg/dl. Of the 150 study subjects 111 (74%) were hypomagnesemic with an average serum magnesium level of 1.41 (±0.18) mg/dl, 38 (25.33%) subjects were normomagnesemic with an average serum magnesium level of 1.95 (±0.22) mg/dl, 1 (0.67%) subject was...
hypermagnesemic with a serum magnesium level of 2.7 mg/dl. The serum magnesium levels of the hypomagnesemic and normomagnesemic individuals were significantly different with a p value of <0.001.

The average serum magnesium level in the female study subjects was 1.5 (±0.29) mg/dl while the average serum magnesium level in the male study subjects was 1.58 (±0.32) mg/dl. The difference between the two groups was not significant with a p value of 0.138.

The average APACHE II score of the study cohort was 26.87 (±6.95) with a median score of 26.

The average APACHE II score for female subjects was 27.55 (±6.48) while the average APACHE II score for the male subjects was 26.58 (±7.15). The difference between the two groups was statistically insignificant with a p value of 0.425.

The average number of days of stay in MICU for the study cohort was 6.53 (±3.02) days with median number of days of stay being 6 days.

The average number of days of ventilation among the ventilated patients were 5.24 (±2.58) with the median number of days being 5.

![Figure 1: Serum Magnesium level vs Age. r value = -0.339 (p=0.000)](image1.png)

Serum magnesium levels show and inverse and significant correlation with Age of the subjects with an r value of -0.339 (p=0.000) [Figure 1]

![Figure 2: APACHE II scores vs Age. r value= 0.569 (p=0.000)](image2.png)
APACHE II scores also showed a direct and significant correlation with Age of the subjects with an r value of 0.569 (p=0.000) [Figure 2].

![Figure 3: APACHE II score vs Serum Magnesium level. r value= -0.21107 (p=0.01)](image)

The mean APACHE II score among the hypomagnesemic subjects was 27.80 (±6.66) and the mean APACHE II score among the normomagnesemic subjects was 24.26 (±7.23). The difference in APACHE II score among the two groups was significant (p=0.0064). A statistically significant correlation was seen between the serum Magnesium levels and the APACHE II score with an r value of -0.21107 and a p value of 0.01. [Figure 3]

![Figure 4: Days of MICU stay vs Serum magnesium levels. r value= -0.318 (p=0.000)](image)
Among the hypomagnesemic the average number of days of MICU stay were 7.05(±3.25). For the normomagnesemic study subjects the average number of days of MICU stay were 5.03(±1.46). The difference between average length of MICU stay between these two groups was statistically significant with a p value of 0.001.

A statistically significant correlation was seen between the serum Magnesium levels and the number of days of MICU stay with a r value of -0.31809464 and a p value of 0.000 for this correlation. [Figure 4]

![Days of Ventilation Vs Serum Magnesium level](image)

**Figure 5:** Days of Ventilation required vs Serum Magnesium levels. R value= -0.303 (p=.001)

![ROC Curve](image)

**Figure 6:** ROC curve of magnesium as a predictor of mortality. AOC value of 0.708 (p=0.000) with a sensitivity and 1-specificity is 0.704 and 0.329 respectively for a cutoff value of 1.55mg/dl of serum magnesium.
The correlation between APACHE II score and days of MICU stay was non-significant with a r value of -0.008104065 and p value of 0.922.

In the hypomagnesemic group of 91 patients (81.98%) required ventilation as compared to 22 patients (57.89%) of the normomagnesemic group. This difference was statistically significant with a p value of 0.0033.

Among the ventilated patients there was a significant correlation between the magnesium level and the days of ventilation with an r value of -0.303 and a p value of 0.001. [Figure 5]

The patients in the hypomagnesemic group had a mortality of 57.65% as compared to a mortality of 15.79% in the normomagnesemia group. This difference was statistically significant with a p value <0.0001.

The mean serum magnesium levels of patients who recovered from the MICU and were shifted to ward was 1.65 (±0.32) mg/dl. This was significantly different (p value <0.001) from the mean magnesium level of the patients who expired in the MICU 1.45 (±0.27) mg/dl. The ROC curve for serum magnesium as an indicator of mortality had an AOC of 0.708 which puts it on the lower bounds of a good score. For a cut off value of 1.55 mg/dl of serum magnesium level the sensitivity and 1-specificity is 0.704 and 0.329 respectively. [Figure 6]

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Figure 7: ROC curve of APACHE II as a predictor of mortality. AOC value of 0.934 (p=0.000) sensitivity and 1-specificity is 0.873 and 0.101 respectively for a cutoff score of 26.5.

The mean APACHE II score of the patients who recovered and were shifted to ward was 22.20(±4.44) and the mean APACHE score among those who expired in the MICU was
The difference between the groups was statistically significant with a P value of <0.001.
The ROC curve for APACHE II scores as predictor of mortality has an AUC value of 0.934 which is in the region of an excellent score. For a cutoff value of 26.5 which is close to the mean APACHE II score of our study population the sensitivity and 1-specificity is 0.873 and 0.101. (Graph 7)

Among the ventilated patients (n=114) 83 patients required ventilation for less than 6 days and 31 for 6 days or more. The average days of ventilations required in the two groups were 5.89 (±1.14) days and 7.97 (±3.54) days respectively. There was statistically significant difference between the days of ventilations required between the two groups (p value 0.003).

Among the patients ventilated for less than 6 days the mean serum magnesium level was 1.58 (±0.3) mg/dl and among the patients ventilated for more 6 days or more was 1.38 (±0.23) mg/dl. The difference between the groups is statistically significant with a p value of <0.001.

The study group was divided into two groups based on the APACHE II score. The first group had an APACHE II score <= to the median score of 26 (n=80) and the second group with a score >26 (n=70).

The difference between the average apache score of the two groups, 21.5375 (± 3.25) vs 32.95714 (±4.65), was statistically significant with a p value of <0.001.

The average number of days of MICU stay for group1 was 6.24 (±2.58) days as compared to 6.87 (±3.43) days of MICU stay for group 2. The difference in the number of days of MICU stay between these groups was insignificant with a p value of 0.209.

The percentage of subjects in group 1 that required mechanical ventilation during the course of their stay was 62.5% as compared to 91.42% of group 2. This difference was statistically significant with a p value of <0.001.

The difference in average serum magnesium levels between those with a history of alcohol use and those with no history of alcohol use, were not statistically significant.

**Discussion**

In a number of studies, it has been shown that a majority of patients admitted to the intensive care units of hospitals are males and our study also shows the same trend with more than 70% patients being male. Among the study subjects a majority of the subjects, 74%, showed hypomagnesemia, 25.33% showed normal serum magnesium levels and only 1 individual had a serum magnesium level above normal. The percentage of hypomagnesemic patients in our study was more than other studies. In the other studies the prevalence of hypomagnesemia is shown to be between 20% to 65%.[11-13]

There was no statistical difference between the serum magnesium level of male and female members of our study group.

In or study age showed a strong and significant correlation with APACHE II score as expected as it is factor in calculating APACHE II score. This is in correlation with earlier studies.[14]

In our study serum Magnesium level showed a significant and strong inverse relation with age. We could not find any study correlating serum Magnesium levels with age in the critically ill.

The average APACHE II score of the study cohort was 26.87 (±6.95) with a median score of 26. This was higher than the mean APACHE II score of subjects of other such studies.[15-17] In our study the mean APACHE II score for the surviving subjects was 22.20 (±4.44) while the mean APACHE II score of patients that expired in the MICU was 32.06 (±5.38). These scores were again higher than in other studies.[15-17] As expected, an increased APACHE II score showed a very strong correlation with mortality among the critically ill patients. The mortality among patients with an APACHE II score less
than equal to the median APACHE II score of 26 was 11.25% while among the patients with an APACHE II score of 26 was 88.57%. Higher than the median APACHE II score was shown to be an independent risk factor for mortality among the critically ill with an odds ratio of 61.1389 (95% Confidence interval 22.2348 to 168.1134, p value P < 0.0001). This was in concordance with earlier studies but our odds ratio was much higher.\textsuperscript{[12,18,19]}

APACHE II score was also a strong predictor for requirement for mechanical ventilation during the course of MICU stay. We could not find any other study that has used APACHE II score as predictor for requirement for mechanical ventilation. APACHE II score did not show a strong or significant correlation with number of days of admission in MICU days or number of days required on ventilation. Earlier studies have also failed to find any such correlation.\textsuperscript{[20,21]}

APACHE II score showed a strong and significant inverse correlation with serum Magnesium levels. This is in opposition of certain earlier findings which did not find any such significant correlation.\textsuperscript{[22,23]}

Serum magnesium levels showed a strong and a very significant correlation with mortality with the hypomagnesemic group having a mortality of 57.65% as compared to the 18.42% of the normomagnesemic group. Serum magnesium level is an independent risk factor for mortality in critically ill patients with an odds ratio of 7.2624 (95% confidence interval 2.8093 to 18.7743 with a p value of < 0.0001). This is in agreement with a number of earlier studies.\textsuperscript{[23,24]}

In our study serum magnesium level also showed a strong and very significant inverse correlation with number of days of MICU stay in the critically ill patients. These findings vary from the finding of Kiran et. al. but resonate with the findings of Minhua Chen.\textsuperscript{[12,23]} A meta-analysis of 30 full text articles and 6 studies involving 1550 subjects agrees with our findings and shows an inverse correlation between serum magnesium levels and number of days of ICU stay.\textsuperscript{[12]}

Magnesium levels have also shown a strong inverse correlation with requirement of ventilation during the MICU stay among the patients. It also showed strong inverse correlation with number of days of ventilation required by the patients. Both these finding are in agreement with earlier studies.\textsuperscript{[25,26]}

**Conclusion**

Our study shows that serum magnesium has a role as an independent prognostication factor for critically ill patients. Hypomagnesemia at the time of admission is marker for increased mortality and morbidity among critically ill patients. Our study also shows that Serum magnesium level show a strong inverse relationship with APACHE II score. While Serum magnesium levels are an acceptable as a for mortality, morbidity when compared to APACHE II score, it is a superior marker for predicting the length of MICU stay and also in predicting the number of days on ventilation required as compared to APACHE II score. In conclusion we would suggest for inclusion of serum magnesium level as an important diagnostic marker in all critically ill patients for its value in prognostication of ICU patients.

**Shortcomings of the study:**

Our study measures total serum magnesium instead of ionized Mg\textsuperscript{2++}. As Mg\textsuperscript{2++} is the active form of magnesium in the serum measuring Mg\textsuperscript{2++} would have provided with better understanding of the correlation of magnesium with outcomes in critically ill patients.

Our study included 150 subjects. A study with a larger study group will provide results with more validity across the population.

Our study group had only one hypomagnesemic individual which was also a limitation in regards to studying the effect of hypermagnesemia on critically ill patients.
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