Co-Morbidities associated with hypomagnesemia and affecting in-hospital mortality in tertiary care hospital of Sindh Pakistan-2021

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Abstract---Background: Hypomagnesemia may cause severe and fatal complications if not timely diagnosed and properly treated, and associated with increased In-Hospital Mortality. Methods: A case-control study was conducted. The case definition was any patient of any age and sex having hypomagnesemia and admitted to ICU. The controls were taken in 1:2. We defined Hypomagnesemia with less than 1.46mg/dl level of magnesium and In-Hospitals mortality as the primary endpoint. Demographic, risk factor data were taken and analyzed using EPI INFO TM 7. The association was calculated using Odds Ratios and reported at 95% CI and P value less than 0.05. Results: Of 139 patients, 42 were cases. The average age was 53 years (14 to 85 Years ±16 years). Males were 72 (49%) and 78 (66%) participants were from rural setup. Diabetes mellitus was found in 33 (78%) of cases and 44 (46%) in controls, hypertension in 36 (85%) of cases and 41 (42%) of controls, dyslipidemia in 20 (48%) of cases and 37 (38%) of controls, obesity in 26 (62%) of cases and 37 (38%) of control, and anaemia in 28 (67%) of cases and 41 (42%) of control. Hypertension (OR 8.1, 95% CI 3.1-21.2, P Value 0.00), Diabetes Mellitus (OR 4.4, 95% CI 1.9-10.2, P Value 0.00), Sofa Score 2 to 3 (OR 3.2, 95% CI 1.4-7.2, P Value 0.00), Anaemia (OR 2.7, 95% CI 1.2-5.8, P Value 0.00), and Obesity (OR 2.6, 95% CI 1.2-5.5, P Value 0.00) were all significantly associated with the hypomagnesemia. A total of 59 (42%) patients died, of which 35 (59%) had documented hypomagnesemia. In-Hospital Mortality was significantly associated with hypomagnesemia (OR 15, 95% CI 5.9-38.6, P Value 0.00). Conclusions: Hypomagnesemia is common in patient admitted in ICU. Hypertension, Diabetes Mellitus and Anaemia tend to increase the frequency of hypomagnesemia in patient who are severely ill and In-Hospital Mortality.

Keywords---Magnesium, Hypomagnesemia, Critical Illness, Intensive Care Unit and In-Hospital Mortality.

Introduction

Magnesium (Mg) is placed at the fourth position among the positively charged ion in the human body, and the second most abundant intracellular ion with a positive charge preceded by potassium. It plays an essential physiological role in many functions of the body. Magnesium also regulates enzymes controlling intracellular calcium, which ultimately affects smooth muscle vasoconstriction, important to the underlying pathophysiology of several critical illnesses. Several diseases and clinical conditions, also various medications such as antibiotics, antihypertensive agents, and proton pump inhibitors may lead to magnesium loss and hypomagnesemia. Hypomagnesemia may have serious implications in critically ill patients as the low level of magnesium activates neuroendocrine pathways, which in turn increases the hospital duration as the pathway starts the stress response in critical patients. It is well documented that critically ill patients are found to have an association between hypomagnesemia and an
increase in the need for mechanical ventilation and also days of mechanical ventilation\textsuperscript{5}.

Mg level assessment is difficult because Mg is mostly intracellular and no simple method exists to measure total body Mg\textsuperscript{6}. The practice of measuring magnesium in blood serum alone has been questioned because Mg is predominantly a cofactor in intracellular metabolic activities and over 99\% of the whole body's Mg is intracellular. Instead, techniques for measuring total cellular Mg in erythrocytes (tMge) have been developed\textsuperscript{7}.

However, intracellular ionized Mg concentration is physiologically much more relevant, and the question of whether ionized Mg should be measured in clinical practice has been raised. Different studies have shown that, depending on the population studied and the tMgs threshold value chosen, the incidence of hypomagnesemia ranges from 15\% in critically ill COPD patients\textsuperscript{8} to 53\% in postoperative ICU patients\textsuperscript{9}. The high prevalence of hypomagnesemia, based on tMgs can probably be explained by Mg shift from extracellular to intracellular compartments, whereby iMg2+s concentration can remain unchanged, in contrast with tMgs. A study by K Okubo et al confirms that changes in magnesium level in a critically ill patient are not comparable by tMg measurements only\textsuperscript{10} but it needs iMg concentration which are very difficult to measure. This finding shows that iMg2+ measurement is preferred to tMgs measurement in clinical circumstances (like sepsis) where aberrant albumin and protein concentrations are anticipated. As a result, if tested directly, iMg2+ would be the best predictor of the actual magnesium level.

There are ample evidence that hypomagnesemia is directly related to in hospital mortality and longer ventilation support\textsuperscript{11}. Comorbid patients having more than two illnesses are at risk of bad outcomes. Patients who are admitted to ICU have high losses of Magnesium from Urinary and Gastrointestinal routes\textsuperscript{12}, therefore measuring magnesium properly in critically ill patients will reduce the mortality and ICU stay. In the Asian country, Bangladesh it was documented by Mamun GM et al. that magnesium levels were a well-established cause of in-hospital mortality in severely ill patients of diarrhoea\textsuperscript{13}. As the genetics, way of life, and eating habits of the Pakistani people differ from those of the rest of the world, this study intends to ascertain the risk factors which lead to hypomagnesemia in order to establish the local perspective.

Therefore the current study is planned to know the risk factors which cause hypomagnesemia and to identify the effect on in-hospital mortality. Moreover, in light of the information obtained from this study, an effective management plan will be developed giving hypomagnesemia prime importance.

**Methods**

A case-control study was conducted from December 2020 to June 2021 at the Department of Medicine, Abbasi Shaheed Hospital, Karachi. All the admission to the respiratory ICU unit were included in the study and 42 cases were identified by using case definition for case selection that any patient of any age and sex having hypomagnesemia and admitted to ICU for > 3 hours with sepsis (SOFA
score ≥ 2) during 1 December 2020 to 30 June 2021. The controls were taken from the same hospital that did not have hypomagnesemia in the ratio of 1:2. Those cases which were having hypo or hyperthyroidism, pregnant women, history of blood transfusion and malabsorption, those who were on calcium or magnesium supplements, and patients having any comorbidities like stroke, chronic renal failure, chronic obstructive pulmonary disease, asthma, congestive heart failure, myocardial infarction, and chronic liver disease have been excluded. We defined Hypomagnesemia as a laboratory assessment of blood magnesium with less than 1.46mg/dl level of magnesium in blood. And in hospitals mortality was defined as the primary end point.

A brief history of demographic data (age, gender, and residence status) and ICU admission duration were taken. The blood samples were collected in a sterile manner and sent to the laboratory to determine the serum magnesium levels. Patients were labeled as having hypomagnesemia as per the operational definition. The data on demographic variables (age, financial income status, occupational status, height, weight, BMI, and duration of admission to ICU) and risk factor variables (diabetes mellitus type II, hypertension, dyslipidemia, obesity status, anemia status, and in-hospital mortality) were collected by using a structured questionnaire.

Data were analyzed using EPI INFO TM 7. Mean and standard deviation was calculated for continuous variables such as age, height, weight, BMI, serum magnesium level, and ICU admission duration. Frequency and percentages were calculated for categorical variables like gender, residence status, diabetes mellitus type II, hypertension, dyslipidemia, obesity status, anemia status, smoking status, financial income status, occupational status, hypomagnesemia and in-hospital mortality. The outcome variable was Hypomagnesemia and the dependent variable was diabetes mellitus type II, hypertension, dyslipidemia, obesity status, anemia status, hypomagnesemia, and in-hospital mortality. The association between the dependent and independent variable were calculated using Odds Ratios and reported at 95% CI and P value less than 0.05.

Results

A total of 139 patients were entered in the final analysis. Of which 42 were cases, meeting the case definition and two control were taken for each case (n=97). The average age in our study was 53 years (Range 14 to 85 Years) with a standard deviation of ±16 years. As is shown in Table 1, Males were 72 (49%) and 57 (51%) were female. The areas-wise distribution showed 78 (66%) participants were from rural set up and 61 (34%) of participants were of urban residence. The duration of ICU admission showed that out of 139 patients, 118 (85%) were admitted for more than 6 hours in ICU and 21 (15%) were admitted to ICU for less than 6 hours. The mean BMI was 25±5 kg/m2, height was 64±3.4 inches and weight was 66±13 kg in our study.
<table>
<thead>
<tr>
<th>Co-Morbidity</th>
<th>Cases (n=42)</th>
<th>Control (n=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes</td>
<td>33  (78%)</td>
<td>9   (22%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36  (85%)</td>
<td>6   (15%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>20  (48%)</td>
<td>22  (52%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>26  (62%)</td>
<td>16  (38%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>28  (67%)</td>
<td>14  (33%)</td>
</tr>
<tr>
<td>Sofa Score &gt;3</td>
<td>31  (73%)</td>
<td>11  (27%)</td>
</tr>
<tr>
<td>Sofa Score between 2 to 3</td>
<td>16  (38%)</td>
<td>26  (62%)</td>
</tr>
</tbody>
</table>

Out of 139 total patients, 59 (42%) patient died. Among those who died 35 (59%) had been having documented hypomagnesemia whereas 24 (41%) had not been having hypomagnesemia. In Hospital Mortality was significantly associated with hypomagnesemia as the patients who had documented hypomagnesemia were 15 times likely to die as compared to the controls (OR 15, 95% CI 5.9-38.6, P Value 0.00) as is shown in table 3.
Table 3 In Hospital Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n=42)</th>
<th>Control (n=97)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>In Hospital Mortality</td>
<td>35 (83%)</td>
<td>7 (17%)</td>
<td>24 (25%)</td>
<td>73 (75%)</td>
<td>15</td>
</tr>
</tbody>
</table>

Among comorbidities, Hypertension was found in 36 (85%) of cases as compared to control 41 (42%). The cases with hypertension were 8.1 times more likely to develop hypomagnesemia (95% CI 3.1-21.2, P Value 0.00). Diabetes Mellitus was the second most documented comorbidity which had been associated with the development of hypomagnesemia. It was found in 33 (78%) of cases versus 44 (946%) of control (OR 4.4, 95% CI 1.9-10.2, P Value 0.00). Sofa Score 2 to 3 (OR 3.2, 95% CI 1.4-7.2, P Value 0.00), Anaemia (OR 2.7, 95% CI 1.2-5.8, P Value 0.00), and Obesity (OR 2.6, 95% CI 1.2-5.5, P Value 0.00) were all significantly associated with the development of hypomagnesemia. However, increasing Sofa Score > 3 and Dyslipidaemia were statistically not proven as the risk factor for the development of hypomagnesemia among hospital patients as is shown in table 4.

Table 4 Factor affecting Hypomagnesaemia in ICU Patients

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Cases (n=42)</th>
<th>Control (n=97)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>36 (85%)</td>
<td>6 (15%)</td>
<td>41 (42%)</td>
<td>56 (58%)</td>
<td>8.1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>33 (78%)</td>
<td>9 (22%)</td>
<td>44 (46%)</td>
<td>53 (54%)</td>
<td>4.4</td>
</tr>
<tr>
<td>Sofa Score between 2 to 3</td>
<td>16 (38%)</td>
<td>26 (62%)</td>
<td>45 (46%)</td>
<td>52 (54%)</td>
<td>3.2</td>
</tr>
<tr>
<td>Anemia</td>
<td>28 (67%)</td>
<td>14 (33%)</td>
<td>41 (42%)</td>
<td>56 (58%)</td>
<td>2.7</td>
</tr>
<tr>
<td>Obesity</td>
<td>26 (62%)</td>
<td>16 (38%)</td>
<td>37 (38%)</td>
<td>60 (62%)</td>
<td>2.6</td>
</tr>
<tr>
<td>Sofa Score &gt;3</td>
<td>31 (73%)</td>
<td>11 (27%)</td>
<td>43 (44%)</td>
<td>54 (56%)</td>
<td>2.2</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>20 (48%)</td>
<td>22 (52%)</td>
<td>29 (30%)</td>
<td>68 (70%)</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Discussion

Lack of magnesium is known as Hypomagnesemia. If not promptly detected and effectively treated, hypomagnesemia may result in serious and sometimes deadly consequences and is linked to higher mortality. We found in our study that hypomagnesemia was common which are consistent with an observational study on 102 medical ICU patients by Reinhart et al. They showed that hypomagnesemia was present in 20% of patients, and of all ions, Mg had the highest prevalence of abnormal values\(^{16}\). Another cohort study by Zeineldin showed that, on ICU admission, 57% of patients had hypomagnesemia and hypomagnesemia was associated with long ICU stay as well as mortality\(^{17}\). The longer stay of patients with hypomagnesemia patients had also been documented in many studies along with the frequent need for mechanical ventilator support (73% (38 of 52) vs. 53% (22 of 41), P < 0.05), longer duration of mechanical ventilation (average 5 days versus 3 days), increased incidence of sepsis (twice) and higher mortality (twice) compared to patients with normal Mg levels\(^{18}\). This is consistent to our study findings.
It has been also been documented by recent research that COVID-19 pneumonia has also been having synergistic effect with hypomagnesemia. Razieh Avan, Afrooz Mazidimoradi and Hamid Salehiniya have documented that COVID-19 severely ill patients should be screened for magnesium and this laboratory documentation should be included in the routine markers of COVID-19 infection\(^{19}\). We have also found in our study that magnesium is among the major causes of severity of respiratory diseases in critically ill patients, although we have not included patients with COVID-19 in our study. However, a study done by Mitra Kazmikehromi and colleagues showed contrasting results for the association of COVID-19 severity and magnesium level in the same setting as we have adopted\(^{20}\).

Past literature reviewed revealed that hypomagnesemia is a key biochemical component contributing to in-hospital mortality. There are significant disparities in mortality between ICU septic patients with hypomagnesemia and those with normomagnesemia, according to a 2022 observational study by Pranav Ravi Kulkurani et al (81% versus 14%)\(^{21}\). We have also documented same finding in our study.

In a study done by Cojocaru et al, in which they have assessed sepsis patients. They documented that Mg level was severely decreased in septic patients\(^{22}\). We have also concluded that cases have severely low Mg levels however comorbidities are mainly discussed in our study design. Therefore every patient in ICU needs proper attention towards Mg level irrespective of the cause of the hospital admission. The study of Cojocaru et al has also documented that Mg concentration fluctuated in these patients irrespective of the cause of the hospital admission and tend to increase the hospital stay longer than other patients.

Our finding of comorbidities and in-hospital mortalities are widely studied in the current literature. However, the role of hypomagnesemia in comorbid critical patients is a new concept. We have found that Diabetes Mellitus, Hypertension, Anaemia, and Dyslipidaemia are all prevalent comorbidities that are accompanied by the severity of the patients admitted to the ICU. It is documented by many studies that hypomagnesemia is a predictor of progression in chronic kidney diseases\(^{23}\). In children, hypomagnesemia is also associated with extended attacks of asthma making magnesium level a sensitive marker for the severity of asthma, which has been evident by measurements by pulmonary function tests\(^{24}\). We have also concluded same that hypomagnesemia could be a possible reason for these enhanced mortalities in ICU patients and can be referenced as a predictor for critical patients who have comorbidities as well.

The major strength of our study is that we demonstrated the role of magnesium in busy hospital catering populations all over the country. The strict inclusion criteria, follow-up of the patients, and laboratory evidence are all among the strength of the study. We have limitations in that the hospital setting was chosen because critically ill patients are usually hospitalized. This study was an attempt to discover the effect of the cation which is almost neglected. Our findings are consistent and we found that magnesium should be considered especially in critically ill patients in future courses.
Conclusions

Hypomagnesemia is common in patient admitted in ICU. Chronic diseases like Hypertension, Diabetes Mellitus and Anaemia tend to increase the frequency of hypomagnesemia in patient who are severely ill. Ultimately the risk of death increases in severely ill patient patients after the development of hypomagnesemia. Further clinical trials and critical evaluation of empiric Mg replacement strategies is needed.

List of Abbreviations
ICU: Intensive Care Unit; BMI: Body Mass Index; CPSP: College of Physician and Surgeon of Pakistan; Mg: Magnesium; mm: tsMg: Total Serum Magnesium; Millimole; dl: decilitre; mg: milligram; JPMC: Jinnah Post Graduate Medical Centre, APACHE: The Acute Physiology and Chronic Health Evaluation;

Declarations
Ethics approval and consent to participate were taken.

Consent for publication
Not applicable.

Availability of data and materials
The datasets used and/or analyzed during the current study are available at the DHO Office Tharparkar (dr.sandeepguriro@gmail.com) on a reasonable request. However the data is also present at url as follow; https://figshare.com/account/items/23703459/edit and at DOI 10.6084/m9.figshare.23703459

Competing interests
The author (s) declares that they have no competing interests.

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Authors' Contributions
Conceptualization: DSM, DAAK, DSS. Data curation: DSAM, DSM, DSKM. Formal analysis: DSKM.DSAM Funding acquisition: DAAK, DSM. Methodology: DSM, DAAK.DSMK Project administration: DSM, DAAK, Writing - original draft: DSM, DSKM, DSAM, DHAJ. Writing - review & editing: DSAAK, DSS.MSAM, MHD. All authors reviewed and approved the manuscript.
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