Hypomagnesemia as a predictor of mortality in Critically Ill Pediatric Patients

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Abstract: **Objectives:** To detect prevalence of hypomagnesemia in critically ill children, its association with sepsis and electrolyte abnormalities and to correlate this with mortality. **Background:** Hypomagnesemia is a significant and under-recognized electrolyte abnormality in critically ill children. It can lead to potentially fatal complications. **Material and Methods:** This is a cross over case control study done at the pediatric intensive care unit (PICU) of Menoufia university Hospital from April 2015 to May 2016. We studied 100 patients who met the inclusion criteria. Patients under the study were managed and treated according to their clinical status and took their supportive traditional treatment. **Results:** Prevalence of hypomagnesemia in critically ill pediatric patients was 59%. Patients with hypomagnesemia had longer ICU stay (10.16 days vs. 6.04 days, p value = 0.007), higher PRISM score (25.83 vs 19.68, p value <0.001), more frequent need for ventilation (76.3% vs. 36.6 %, p value <0.001), higher mortality (57.6% vs. 29.3% (p value = 0.008), higher incidence of electrolyte abnormalities like hypokalemia (62.71% vs. 34.14%, p = 0.004) and hypocalcemia (71.18 % vs. 41.46 %, p = 0.002) and more frequent association with sepsis (67.8% vs. 32.2%, p=< 0.001) than patients with normal magnesium level. By analysis of the Receiver operating characteristic curve (ROC curve), we found an area under the curve (AUC) of .638 for Mg for diagnosis of sepsis while C-reactive protein (CRP) had an AUC of.948. As regard prognosis, Mg had an AUC of 0.576 for prediction of mortality whereas the AUC for PRISM score was 0.811 and for CRP was 0.716. Logistic regression analysis showed that hypomagnesemia is a significant predictor for mortality among critically ill children (p value = 0.028) and OR = 3.180 (0.854-7.965). **Conclusion:** Hypomagnesemia is common and is associated with high incidence of morbidity and mortality in critically ill children so, routine monitoring is vital for timely diagnosis.
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1. Introduction:

Magnesium (Mg^{+2}) is important for many cellular functions. It acts as a cofactor for more than 300 enzymatic reactions mainly involving transfer of phosphate group, for example, formation of ATP. It also maintains neuromuscular excitability and is important for maintenance of cardiac function. Although hypomagnesaemia is common in critical illness, it is frequently overlooked. **[1]**

Magnesium is critically important in maintaining normal cellular function. Symptomatic magnesium depletion is often associated with multiple biochemical abnormalities, including hypokalemia, hypocalcaemia, and metabolic acidosis. As a result, hypomagnesaemia is sometimes difficult to attribute solely to specific clinical manifestations. Organ systems commonly affected by magnesium deficiency are cardiovascular, central and peripheral nervous systems. Skeletal, hematologic, gastrointestinal, and genitourinary systems are also affected**. [2]**

Critical illness is any disease process which can cause physiological instability leading to disability or death within minutes, hours or days. **[3]**

The main purpose of the PICU is to prevent mortality by intensively monitoring and treating at risk critically ill children. The capability to estimate patient risk of death is extremely important because such estimate would be useful in achieving many different goals such as assessing patient's prognosis, ICU performance, ICU resource utilization, evaluating therapies, controlling and matching severity of illnesses in clinical studies.**[4]**

The aim of that study was to detect prevalence of hypomagnesemia among critically ill children, its association with length of stay in the pediatric intensive care unit, need for mechanical ventilation, electrolyte abnormalities and sepsis and to correlate this with morbidity and mortality.

2. Patients and methods:

Patients:

We conducted the current cross-over case-control upon 100 critically ill children admitted to the PICU of Menoufia University Hospital from April 2015 to May 2016. We were attached to the time frame of our study so we selected the cases from the total number admitted this year to our pediatric intensive care unit which was 176 cases and after applying the exclusion criteria, the number has been reduced to 100. Criteria for eligibility in this study

included: (1) Age beyond the neonatal period up to 18 years. (2) Critical illness requiring ICU admission. (3) Parental consent. The exclusion criteria included: (1) Patients in the neonatal period or those older than 18-years old. (2) Lack of parental consent. (3) Patients who received magnesium supplementation before transfer to the intensive care unit.

Methods:

For each patient, a complete diagnostic work-up was performed including thorough history and physical examination. Physical examination included: recording heart rate, respiratory rate, blood pressure, pupillary reaction, and Glasgow coma scale. Laboratory Work-up included: assessment of arterial blood gases, random blood glucose, complete blood count, C-reactive protein, serum electrolytes including magnesium level, blood cultures, liver and kidney function tests, prothrombin and partial thromboplastin times. Cultures of other body fluids, like cerebrospinal fluid (CSF) and urine, were done when clinically required. Chest radiograph, brain CT, and other laboratory or radiological investigations were performed when indicated. In addition, a severity score was calculated which was the Pediatric Risk of Mortality (PRISM) score.**[5]**

PRISM score was automatically calculated from the website: *http://www.sfar.org/scores2/prism2.php* within 24 hours of admission together with assessment of serum Mg^{+2}. Serum Mg level was determined using Calmagite Colorimetric method. Patients were classified into groups based on this level as patients with serum magnesium < 1.5 mg/dl were considered hypomagnesemic and were taken as cases while patients with level >1.5 mg/dl and less than 2.3 mg/dl were considered normomagnesemic and were taken as controls. Primary outcome measure was occurrence of death during PICU admission. Secondary outcome measures included length of PICU stay and need of mechanical ventilation.

Ethical approval:

All the procedures performed in that study were in accordance to the ethical standards of Menoufia university institutional research committee.

Statistical analysis:

Data were given as mean ± standard deviation and also as a range. Categorical data were analyzed by chi- square test. Continuous variables were compared by t-test but for continuous variables with skewed distribution or when the groups are small, we used Mann–Whitney-U-test. Also, Mann–Whitney-U-test was used for post hoc analysis. Chi square test ($\chi 2$), student (t) test and Mann–Whitney-U-test were used as tests of significance. The diagnostic powers of hypomagnesemia and other variables were evaluated by the receiver operating characteristic (ROC) curve with the Youden index used to select the optimal cut-off values. We used IBM SPSS software version 20.0 (SPSS, Inc., Chicago, IL, USA) for statistical analysis. The results were evaluated in 95% confidence interval. P value <0.05 was considered significant. Binary logistic regression analysis was done to determine the predictivity of our regression model relying upon mortality as a dependent variable, and other parameters as potential independent variables through estimation of Odds Ratio (OR), 95% CI, and significance level at 95%.

3. Results:

As regard to serum magnesium level, we found that 59 of the 100 studied patients were hypomagnesemic and their magnesium level ranged from 0.8-1.4 mg /dl and 41 children were normomagnesemic and their level ranged from 1.5 mg /dl - 2.3 mg /dl). **Table (1)**.

Ages of hypomagnesemic children ranged from 45 days to 15 years with mean (±SD) age of 4.44 ± 4.45 years while the ages of children with normal level ranged from 45 days to 14 years with mean (±SD) age of 4.12 ± 4.37 years.39 patients (66.1%) of the hypomagnesemic group were males and 20 (33.9%) were females while in the normomagnesemic one 23 patients (56.1%) were males and 18 patients (43.9%) were females **Table (1)**.

As regard anthropometric measures, Weight of the cases in the hypomagnesemic group ranged from 4 kg to 55 kg with mean weight (± SD) of 16.10 ±11.54 while in the normomagnesemic one it ranged from 3 kg to 45 kg with mean weight (± SD) of 15.05 ± 10.62 kg. Height ranged in the hypomagnesemic group from 45 cm to 150 cm with mean (± SD) of 93.29±31.49 cm and in the normomagnesemic one it ranged from 45 cm to 160 cm with mean (± SD) of 92.17 ± 32.57 cm **Table (1)**. BMI ranged from 8.87 to 28.06 in the hypomagnesemic group with mean (± SD) of 7.85±3.38 while in the normomagnesemic one it ranged from 11.11 to 21.42 with mean (± SD) of 7.27±2.74 **Table (1)**.

As regard to length of stay in the PICU, the mean duration of stay of patients with hypomagnesemia (± SD) was 10.16±9.03 days while that of patients with normal level (± SD) was 6.04 ± 6.43 days (p value = 0.007) **Table (1)**.

Mean PRISM score in the hypomagnesemic group (± SD) was 25.83±5.23 with while mean PRISM score in the normomagnesemic one (± SD) was 19.68±6.06 with **Table (1)**.

As regard to need of ventilation, 76.3 % of patients with hypomagnesemia needed ventilator support in comparison to only 36.6 % of patients with normal level (p value = <0.001).

Mortality rate in the hypomagnesemic group was 57.6 % while in the normomagnesemic one it was

29.3 % (p value = 0.008) **Table (1)**. **This table shows that:** The studied groups were matched regarding age, sex and anthropometric measures. There was significantly higher length of stay in the pediatric intensive care unit, higher PRISM scores, increased need for ventilation and higher prevalence of mortality in hypomagnesemic group than normomagnesemic one.

Table (1): Socio-demographic and clinical characteristics of the studied groups.

Demographic data	Hypomagnesemic group (n=59) Mean± SD	Normomagnesemic group (n=41) Mean± SD	Test of significance	P value
-Age (years) -Range:	4.44 ± 4.45 45 days – 15 years	4.12 ± 4.37 45 days – 15 years	1118.5*	0.523
sex: -Male -Female	 39 (66.1%) 20 (33.9%)	 23 (56.1%) 18 (43.9%)	1.028**	0.311
-Body weight (kg) -Range:	16.10 ± 11.54 4 - 55 kg	15.05 ± 10.62 3 - 45 kg	1138.500*	0.618
Height(cm) -Range:	93.29±31.49 45 cm - 150 cm	92.17±32.57 45 cm - 160 cm	1160*	0.728
-BMI -Range:	7.85 ± 3.38 8.87-28.06	7.27±2.74 11.11- 21.42	1126*	0.558
-Length of stay in the PICU (days) -Range:	10.16 ± 9.03 1 – 35 days	6.04 ± 6.43 1-30 days	823.500*	0.007
-PRISM score -Range:	25.83 ± 5.23 13 – 33	19.68 ± 6.06 13-30	594.500*	<0.001
-Mortality risk of according to PRISM score -Range:	61.90 ± 21.41 11% - 88.6%	35.87 ± 26.34 11 % - 77.2 %	595**	<0.001
-Need for ventilation: -Yes -No	 45 (76.3) 14 (23.7)	 15 (36.6) 26 (63.4)	15.87**	<0.001
-Mortality: -Died -Survived	 34 (57.6) 25 (42.4)	 12 (29.3) 29 (70.7)	7.83**	0.008

*, **Mann Whitney U test**;**, **Chi square test**; **BMI**, body mass index; **SD**, standard deviation; **P-value ≤ 0.05** is considered significant; **P-value > 0.05** is considered non-significant.
N.B: The term height is for children more than 2 years. For children less than 2 years, we measured length.

There were significantly higher levels of CRP in the hypomagnesemic group than that were observed in the normomagnesemic one with p value of 0.004 **Table (2)**.

We also found that patients with low serum magnesium had lower albumin level than those with normal magnesium with p value of 0.036 **Table (2)**.

As regard to electrolyte disturbances, we found that incidence of hypokalemia was 62.71 % in the hypomagnesemic group in comparison to 34.14% in the normomagnesmic one **Table (3).**

As regard to serum calcium levels, incidence of hypocalcemia was 71.18 % in the hypomagnesemic group higher than 41.46 % which was observed in the normomagnesemic one **Table (3).**

There was higher prevalence of sepsis among cases with hypomagnesemia (67.8%) than among cases with normal magnesium level (32.2%) with p value <0.001 **Table (4)**.

Performance of Mg^{+2} relative to classic inflammation and sepsis was tested through ROC curve analysis; CRP was found to be the most superior as it achieved an AUC of 0.948 while Mg had an AUC of.638. The best magnesium cutoff point for prediction of sepsis in our study was 1.35 mg/dl with sensitivity of 69 % and specificity of 56% **Table (5) and figure (1)**.

Further analysis by ROC curve was performed to test the predictive power of Mg^{+2} along with other relevant factors for mortality. Mg^{+2} achieved an AUC of 0.576 (p = 0.049). Best Cut-off level for prediction of mortality in our study was 1.25 mg/dl with sensitivity of 61% and specificity of 71%. On the other hand, CRP and PRISM score can highly predict

mortality with values of (AUC= 0.716, p = <0.001) and (AUC= 0..811, p = <0.001) respectively **Table (6) and figure (2).**

We also found that: high PRISM score, elevated CRP level, hypomagnesemia, hypoalbuminemia, hypokalemia, sepsis and need for ventilation were the potential risk factors for mortality among the studied patients **Table (7).**

Logistic regression analysis showed that that hypomagnesemia was a significant predictor for patients' mortality (p value (0.028). Patients with hypomagnesemia were 3.18 times more at risk of mortality than patients with normal magnesium level: OR 3.180 (0.854-7.965). Also, need for mechanical ventilation and elevated PRISM score can significantly predict mortality.

Regarding other risk factors for mortality (as elevated CRP level, hypoalbuminemia, hypokalemia, and sepsis), we found that they were associations not causations of mortality as p value was >0.05 **Table (8).**

Table (2): Pearson correlation between levels of serum Magnesium and the results of laboratory investigations in the studied groups.

Laboratory investigations	Hypomagnesemic (n=59) Mean± SD	Normomagnesemic (n=41) Mean± SD	Test of significance	P value
Hb (g/dl)	**8.32±1.61**	**8.84±1.78**	**-1.518-****	**.132**
CRP (mg/dl)	**69.89±31.17**	**46.64±34.13**	**410.50***	**.004**
Creatinine (mg/dl)	**0.97±0.75**	**0.95±0.88**	**1160.50***	**.730**
Bilirubin (mg/dl)	**1.05±0.99**	**0.98±1.34**	**1006.00***	**.152**
Albumin (g/dl)	**3.02±0.89**	**3.37±0.71**	**-2.121-****	**.036**
Na (mEq/l)	**134.94±6.27**	**132.27±21.70**	**.897****	**.372**
K (mEq/l)	**3.18±0.84**	**3.58±0.69**	**-2.476-****	**.015**
Ca (mg/dl)	**8.01±1.71**	**9.04±1.50**	**-3.104-****	**.002**

*, **Mann Whitney U test**;**, **Chi square test**; **SD**, standard deviation; **Hb**, hemoglobin; **CRP**, C-reactive protein; **Na**, sodium; **K**, potassium; **Ca**, calcium; **P-value ≤ 0.05** is considered significant; **P-value > 0.05** is considered non-significant.

This table shows that: There were significantly higher levels of CRP in hypomagnesemic group than normomagnesemic one. On the other hands, there were significantly lower levels of serum albumin, K and Ca in the hypomagnesemic group.

Table (3): Comparison between hypomagnesemic and normomagnesemic groups regarding levels of serum albumin, potassium and calcium.

Variables	Hypomagnesemic (n=59) No (%)	Normomagnesemic (n=41) No (%)	χ^2	P
S. Albumin(g/dl):				
- Normal	22 (37.28 %)	25 (60.97 %)	5.44	**.019***
- Low	37 (62.71 %)	16 (39.02 %)		
K (mEq/l):				
- Normal	22 (37.28 %)	27 (65.85 %)	7.89	**.004***
- Low	37 (62.71 %)	14 (34.14 %)		
Ca (mg/dl):				
- Normal	17 (28.81 %)	24 (58.53 %)	8.83	**.002***
- Low	42 (71.18 %)	17 (41.46 %)		

χ^2, Chi square test; **n,** number; **P-value ≤ 0.05** is considered significant; **P-value > 0.05** is considered non-significant.

This table shows that: there were significantly higher prevalence of cases of lower serum levels of albumin, K and Ca in the hypomagnesemic group than the normomagnesemic one.

Table (4): Comparison between hypomagnesemic and normomagnesemic groups as regard incidence of sepsis:

Variable	Hypomagnesemic (n=59) No (%)	Normomagnesemic (n=41) No (%)	$\chi 2$	P value
Sepsis **-Septic cases:** **-Aseptic cases:**	**40 (67.8)** **19 (32.2)**	**12 (29.3)** **29 (70.7)**	**14.38**	**< 0.001**

χ^2, Chi square test; **n,** number; **P-value ≤ 0.05** is considered significant; **P-value > 0.05** is considered non-significant.

This table shows that: there was significantly higher prevalence of sepsis in the hypomagnesemic group than the normomagnesemic one.

Table (5): Area under the curve (AUC), Cutoff level, Sensitivity and Specificity of Magnesium and CRP for prediction of sepsis in the studied cases.

Test Result Variable(s)	AUC	SE	P value	Confidence interval CI		Cut off value	Sensitivity	Specificity
				Lower	Upper			
CRP	**.948**	**.024**	**<0.001**	**.901**	**.995**	**49**	**70 %**	**30%**
Mg	**.638**	**.047**	**0.041**	**.391**	**.790**	**1.35**	**69 %**	**56%**

CRP, C-reactive protein; **Mg**, magnesium; **AUC**, area under the curve; **CI**, confidence interval; **P-value ≤ 0.05** is considered significant; **P-value > 0.05** is considered non-significant.

Table (6): Cut off point, Area under the curve, sensitivity and specificity of magnesium, CRP and PRISM score in predicting mortality.

Test Result Variable(s)	AUC	p	Confidence interval CI		Cut off value	Sensitivity	Specificity
			Lower	Upper			
CRP	.716	**<0.001**	.600	.833	51	85%	68%
Mg	.576	**0.049**	.318	.675	1.25	61%	71%
Prism Score	.811	**<0.001**	.705	.918	25.50	81%	55%

CRP, C-reactive protein; **Mg**, magnesium; **AUC**, area under the curve; **CI,** confidence interval; **P-value ≤ 0.05** is considered significant; **P-value > 0.05** is considered non-significant.

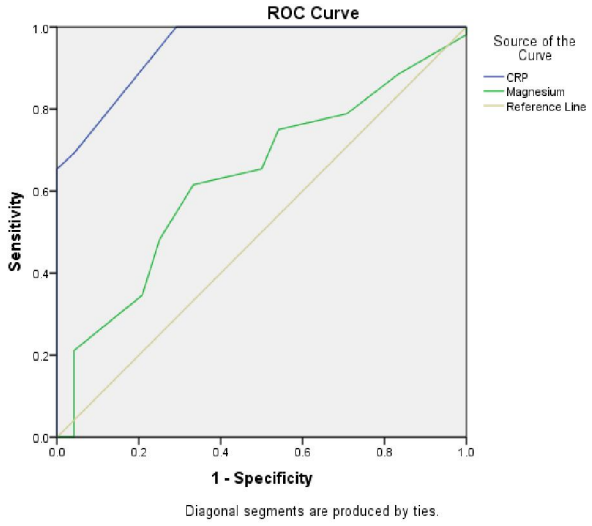

Figure (1): Receiver-operating characteristic (ROC) curve of Mg and CRP for prediction of sepsis in the studied cases.

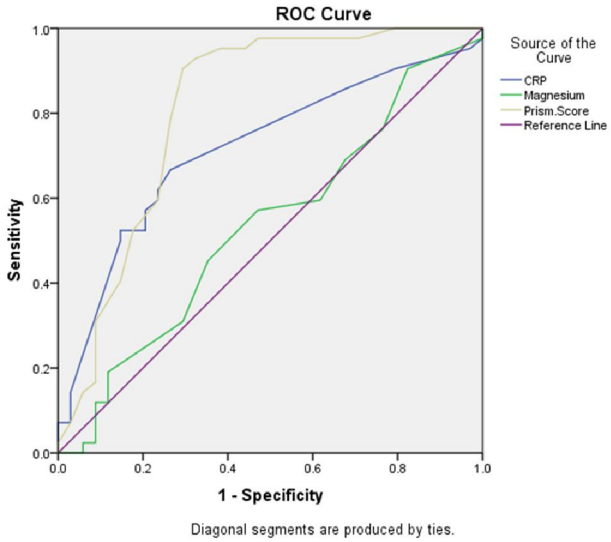

Figure (2): ROC curve of serum magnesium level, CRP and PRISM score for prediction of mortality in the studied patients.

Table (7): Risk factors of Mortality in the studied patients (n=100):

Predictors of Mortality		The studied patients (n=100)		Test of significance	P value
		Dead (n=46) Mean± SD	Survived (n=54) Mean± SD		
Age (years)		4.28±4.52	4.28±4.33	1177*	0.653
BMI		7.33±3.47	7.87±2.83	1068	0.229
Duration of stay in Picu (days)		8.15±8.63	8.76±8.05	1069.5*	0.231
Hb (g/dl)		8.35±1.73	8.71±1.67	1.17**	0.243
PRISM		25.54±5.17	21.41±6.66	3.15**	0.002
Gender:	-Male (52) -Female (48)	30 (65.2) 16 (34.8)	34 (63.0) 20 (37.0)	0.06***	0.815
CRP:	+ve (75) -ve (25)	39 (84.8) 7 (15.7)	36 (66.7) 18 (33.3)	4.35***	0.037
S. creatinine:	-Normal (82) - High (18)	40 (87.0) 6 (13.0)	42 (77.8) 12 (22.2)	1.42***	0.234
S. bilirubin (mg/dl):	-Normal (95) - High (5)	44 (95.7) 2 (4.3)	51 (94.4) 3 (5.6)	0.08***	0.782
S. Albumin (g/dl):	-Normal (49) -Low (51)	17 (37.0) 29 (63.0)	32 (59.3) 22 (40.7)	4.94***	0.023
Na (mEq/l):	-Normal (76) -Low (20) -High (4)	36 (78.3) 9 (19.6) 1 (2.2)	40 (74.1) 11 (20.4) 3 (5.6)	0.78***	0.679
K (mEq/l):	-Normal (50) -Low (50)	18 (39.1) 28 (60.9)	32 (59.3) 22 (40.7)	4.03***	0.045
Ca (mg/dl):	-Normal (42) -Low (58)	16 (34.8) 30 (65.2)	26 (48.1) 28 (51.9)	1.82***	0.177
Mg (mg/dl):	-Normal (39) -Low (56) -High (5)	34 (73.9) 10 (21.7) 2 (4.3)	22 (40.7) 29 (53.7) 3 (5.6)	11.46***	0.003
Sepsis:	-Present (53) -Absent (47)	31 (67.4) 15 (32.6)	22 (40.7) 32 (59.3)	7.08***	0.008
The need for mechanical ventilation:	-Yes (58) -No (42)	37 (80.4) 9 (19.6)	21 (38.9) 33 (61.1)	17.60***	<0.001

*** Mann Whitney U test**; *** * Student t test**;*** * * Chi square test**; **SD**, standard deviation; **BMI**, body mass index; **Hb**, hemoglobin; **PRISM**; pediatric risk of mortality; **CRP**, C-reactive protein **Na**, sodium; **Ca**, calcium; **Mg**, magnesium; **K**, potassium; **P-value ≤ 0.05** is considered significant; **P-value > 0.05** is considered non-significant.

This table shows that: High PRISM score, elevated CRP, hypoalbuminemia, hypokalemia, hypomagnesemia, sepsis and need for mechanical ventilation were the potential risk factors for mortality in the studied cases.

Table (8): Binary logistic regression analysis for predictors of Mortality in the studied cases.

Variable(s)	B	P	OR	95% C.I for OR	
				Lower	Upper
CRP	.020	.258	1.020	.986	1.055
Albumin	-.277-	.631	.758	.245	2.348
K	.046	.930	1.047	.374	2.930
Mg	3.157	.028	3.180	.854	7.965
Sepsis	.067	.961	1.069	.071	16.097
Need for ventilation	-4.657-	.002	.009	.001	.170
PRISM Score	.299	.001	1.349	1.125	1.617
Constant	-8.044-				

B, beta; **P-value ≤ 0.05** is considered significant; **P-value > 0.05** is considered non-significant; **OR,** Odds Ratio; **C.I,** Confidence interval.

N.B: Regarding other risk factors for mortality (as elevated CRP level, hypoalbuminemia, hypokalemia, and sepsis): we found that they were associations not causations of mortality as p value was >0.05.

This table shows that: we found that hypomagnesemia was a statistically significant predictor for patients' mortality: p value (0.028). Binary logistic regression showed that patients with hypomagnesemia were 3.18 times more at risk of mortality than patients with normal magnesium level: OR 3.180 (0.854-7.965). Also, need for mechanical ventilation and elevated PRISM score can significantly predict mortality.

4. Discussion:

Hypomagnesaemia can result in disturbances in nearly every organ system and can cause potentially fatal complications such as coronary artery vasospasm, ventricular arrhythmia, and even sudden death**. [6]**

As regard to serum magnesium level, the prevalence of hypomagnesemia was high as 59 of the 100 studied patients were hypomagnesemic and their level ranged from 0.8-1.4 mg /dl and 41 were with normal level and their level ranged from 1.5 - 2.3 mg/dl. These results were in agreement with **Das et al., [7]** who found that the prevalence of hypomagnesaemia was 53% and that of normomagnesemia was 47 %. In contrast, **Soliman et al., [8]** study on 442 patients found that the prevalence of hypomagnesemia was much lower than normomagnesemia (14 % to 18%). This difference may be due to measurement of ionized magnesium in that study.

Ages of patients with hypomagnesemia ranged from 45 days to 15 years with mean age (± SD) of 4.44 ± 4.45 years while ages of those with normal magnesium level ranged from 45 days to 14 years with mean age (± SD) of 4.12 ± 4.37 years. 39 children (66.1 %) of the hypomagnesemic group were males and 20 (33.9 %) were females, while in the normomagnesemic one 23 children (56.1%) were males and 18 (43.9 %) were females.

As regard anthropometric measures of the studied patients, weight of cases in the hypomagnesemic group ranged from 4 kg to 55 kg with mean weight (± SD) of 16.10 ± 11.54 while in the normomagnesemic one it ranged from 3 kg to 45 kg with mean weight (± SD) of 15.05 ± 10.62 kg. Height ranged in the hypomagnesemic group from 45 cm to 150 cm with mean height (± SD) of 93.29 ± 31.49 cm and in the normomagnesemic one it ranged from 45 cm to 160 cm with mean height (± SD) of 92.17 ± 32.57 cm. BMI ranged from 8.87 to 28.06 in the hypomagnesemic group with mean (± SD) of 7.85 ± 3.38 while in the normomagnesemic one it ranged from 11.11 to 21.42 with mean (± SD) of 7.27 ± 2.74. We found no significant statistical difference between both hypomagnesemic and normomagnesemic groups as regard age, sex or anthropometric measures **Table (1)** and this was in agreement with studies done by **Das et al.,[7], Demircan et al.,[9], and Safavi and Honarmand.[10]**

As regard to length of stay in the PICU, mean duration of stay of patients with low serum magnesium (± SD) was 10.16 ± 9.03 days while that of patients with normal level (± SD) was 6.04 ± 6.43 days. This was in agreement with a study done in india by **Kumar et al., [11]** who found that hypomagnesemia was associated with longer stay in the ICU (5.46 ± 5.75 days) in comparison to (3.93 ± 3.88 days) among patients with normal level. Also, Another prospective observational study over 374 critically ill patients carried out by **Chen et al.,[12]** showed that hypomagnesemia was associated with longer ICU stay (15.98 ± 13.29 days vs. 12.43 ± 7.14

days). This was in contrast to **Limaye et al., [1]**, **Saleem and Haque [13]** and **Hulst et al., [14]** Studies in which there was no significant difference in the duration of stay between patients with low or normal level. This may be due to differences between these studies in sample size, time of research and clinical condition of patients under study as there are many factors that can affect length of stay in an ICU unit**. [15]**

Mean PRISM score in hypomagnesemic patients (± SD) was 25.83 ± 5.23 while mean PRISM score in normomagnesemic patients (± SD) was 19.68 ± 6.06**.** This difference was statistically significant and this denotes presence of high association between disease severity and hypomagnesemia**.** Despite **Soliman et al., [8]** have found lower incidence of hypomagnesemia in his studied group; they found that patients who developed ionized hypomagnesemia during their ICU stay had higher APACHE II score, longer ICU stay and higher mortality rate than other patients! In contrast, **Zafar et al., [17]** did not find significant difference between hypomagnesemic and normomagnesemic patients as regard Acute Physiology and Chronic Health Evaluation (APACHE) which is a severity of disease classification system and one of several ICU scoring systems. This may be due to the small size of that studied sample (only 70 patients). They found higher incidence of electrolyte disturbances, multiorgan dysfunction and mortality among the hypomagnesemic group irrespective of this insignificant ICU stay or APACHE-II score! The authors in that study explained this finding by a strong association between hypomagnesemia and sepsis, a common cause of death in ICU patients.

As regard to need of ventilation, 76.3 % of patients in the hypomagnesemic group needed ventilator support in comparison to only 36.6 % in the normomagnesemic one. Our results are in agreement with **Safavi and Honarmand [10]** study in which hypomagnesemic patients needed mechanical ventilation (58.6%) more frequently than others with normomagnesemia (41.4%). Also **Limaye et al., [1]** found that hypomagnesemic patients have more frequent need of ventilator support (73% vs 53%) with p value of 0.005. That is because hypomagnesemia cause weakness of the respiratory and skeletal muscles and so can cause difficulty of weaning from the ventilator and this can explain higher need for mechanical ventilation and longer PICU stay in the hypomagnesemic group. **[10]**

Mortality rate in the hypomagnesemic group was 57.6 % which was higher than 29.3 % that was observed in the normomagnesemic one. Relationship between hypomagnesemia and mortality varied in-between studies as a higher mortality rate was detected in the hypomagnesemic group when compared to the normomagnesemic one as in studies carried out by **Das et al., [7],** who found 47.2 % incidence of mortality in the hypomagnesemic group vs 23.4 % in the normomagnesemic one, **Atkar et al., [16]** found 60% vs 40 %, **Zafar et al., [17]** found 76.47 % vs 36 % and **Mousavi et al., [18]** found 83.3 % vs 34 %. Also **Limaye et al., [1]** observed that mortality rate in the hypomagnesemic group was 57% when compared to 31 % in the normomagnesmic one. This is due to the significant role of magnesium in maintaining body homeostasis. Also, hypomagnesemia has been associated with many clinical manifestations such as arrhythmias, bronchospasm, seizures, many electrolyte disturbances including hypokalemia, hypocalcemia, hyponatremia, and hypophosphatemia and may be sudden death**.[6]**

Dabbagh et al.,[19] published in 2006 the results of a prospective observational study on 71 patients consecutively admitted to the ICU, and showed that 41 of 71 patients (60%) had hypomagnesemia and daily Mg supplementation > 1 g/day is potentially associated with a lower mortality rate so, the authors suggested an aggressive ICU Mg supplementation protocol as magnesium can lower mortality. **In contrast**, few studies revealed that there was no correlation between hypomagnesemia and increased mortality in acutely critically ill or injured patients as **Hujjgen et al., [20]** who found no correlation between hypomagnesemia and the outcome. This finding may be caused by presence of heterogenicity in different patient populations in every ICU study about hypomagnesemia. Also, **Saleem and Haque [13]** did not observe significant high mortality in hypomagnesemic group when compared to normomagnesemic one. These results may be due to several limitations of that study as it was a single center study, and may not represent the findings at other centers. Also, being a retrospective one; it was not possible to assess all the variables as we did. Also **Ñamendys et al., [21]** found no statistically significant difference in the mortality rate between both groups with or without hypomagnesaemia. That is because they focused to study hypomagnesemia in a certain group of critically ill patients (with hematological malignancies) not in a wide range of diseases as in our study.

As regard to the tested laboratory parameters, there were no significant differences between both hypomagnesemic and normomagnesemic groups in levels of hemoglobin, creatinine, bilirubin or serum sodium but there were highly significant differences between the two groups in levels of serum potassium, calcium, albumin and CRP.

There were significantly higher levels of CRP in the hypomagnesemic group than that were observed in the normomagnesemic one. This was in agreement with **Švagždienė et al., [22]** who also suggested presence of association between hypomagnesemia, oxidative stress and low-grade inflammation. That is because low magnesium levels are linked to systemic inflammation and endothelial dysfunction. Potential pathways include intracellular calcium influx due to low Mg and subsequent phagocytic cell priming, release of neuromediators including substance P and activation of the nuclear factor light chain enhancer of activated b-cells (NFk B) pathway involved in regulation of immune and inflammatory response. Studies including those in animal models have also shown that hypomagnesemia is associated with increased levels of high-sensitivity C-reactive protein (hs-CRP), circulating endothelin, and cytokines, which are indicative of a generalized inflammatory state. **[22]**

Patients with low magnesium also had lower albumin level than patients with normal magnesium (62.71 % vs 39.02 %) and this was in agreement with **Kiran et al., [23]** who found that there was significant association between hypomagnesemia and hypoalbuminemia. That is because about 30% of serum Mg is bound to protein, mainly albumin, so the total measured concentrations of Mg may be affected by hypoalbuminemia**. [24]**

As regard to electrolyte disturbances, incidence of hypokalemia was 62.71% in the hypomagnesemic group in comparison to 34.14% in the normomagnesmic one. This was in agreement with **atkar et al., [16]** who found hypokalemia in 55.7 % of patients with hypomagnesemia and **Das et al., [7]** who found hypokalemia more prevalent in the hypomagnesemic group (81.1% vs. 51.1%). This can be attributed to presence of many disorders that can cause both magnesium and potassium loss such as vomiting, diarrhea, nasogastric suctioning or diuretic use. Also, in state of hypomagnesemia, there is increased loss of potassium from the kidney. Because of the role of magnesium in transmembrane potassium transport; simultaneous correction of hypomagnesaemia is required to correct hypokalemia. **[11]**

As regard to serum calcium levels, incidence of hypocalcemia was 71.18 % among patients with hypomagnesemia and this was higher than 41.46 % that was observed in the normomagnesemic group. This difference was statistically significant. This was in agreement with **Limaye et al., [1]** who found 69% incidence of hypocalcemia in the hypomagnesemic group vs 50% in the normomagnesemic one. Also, **Das et al., [7]** found 81.1 % vs 34 %. That is because hypocalcemia in the hypomagnesemic state involves defect in release and synthesis of the parathyroid hormone. **[25]**

We found more prevalence of sepsis among patients in the hypomagnesemic group (67.8%) than in the normomagnesemic one (32.2%). This was in agreement with **Cojocaru et al., [26]** who studied patients with sepsis and found a significant decrease in serum Mg concentrations (1.26 ± 0.12 mEq/L) in patients with acute bacterial infections than others without evidence of infection (1.69 ± 0.14 mEq/L). That is because Mg ions have an important role in many immunological functions and its deficiency can lead to sepsis. **[27]**

On assessment of the Risk factors for mortality in this study, we found that hypomagnesemia is a significant risk factor (P= 0.003) and this was in agreement with the results of a systematic review done by **Fairley et al., [28]** as they searched MEDLINE, CENTRAL, and EMBASE databases from 1975 to July 2014 for English language articles excluding obstetric, non–intensive care unit based, and specific population (poisoning, cardiothoracic, and neurosurgery) studies. They identified articles on magnesium measurement, associations, and therapy. They identified 34 relevant studies and they found that risk of mortality was significantly increased with hypomagnesemia (odds ratio, 1.85; 95% confidence interval, 1.31-2.60).

In addition, Binary Logistic regression analysis showed that hypomagnesemia is a significant predictor for mortality among critically ill patients; p=0.028 and OR = 3.180 (0.854-7.965). This was in agreement with the results of a study done by **Chattopadhyay et al., [29]** over 62 Peritoneal dialysis patients treated at Long Island College Hospital and showed that serum magnesium was a significant predictor of mortality [relative risk [(RR): 0.142; P = 0.009]. Also, a study in 2014 on 150 critically ill patients in a major tertiary hospital done by **Sari et al., [30]**, found that hypomagnesemia at admission to the intensive care unit is a significant predictor of mortality [P = 0.015 and crude RR = 2.2 (95% CI = 1.19 to 4.06)]. In addition, a systematic review done by **Upala et al., [31]** and included studies that assessed the association between hypomagnesemia and mortality in the critical care setting. These studies were comprehensively searched in MEDLINE and EMBASE databases from their inception to September 2015. From 30 full-text articles, 6 studies involving 1550 participants were included in the meta-analysis. There was a statistically significant higher risk of mortality in critically ill patients who had hypomagnesemia with [RR of 1.90 (95% CI: 1.48–2.44, $P < 0.001$, $I^2 = 63.5\%$)]. Risk for needing mechanical ventilation was also higher in the hypomagnesemia group with RR of 1.65 (95% CI:

1.12–2.43, P = 0.01, I^2 = 84%). Length of ICU stay was also higher in the hypomagnesemia group with mean difference of 4.1 days (95% CI: 1.16–7.04, P = 0.01).

Conclusion:

Hypomagnesemia is common among critically ill children. It is associated with higher need for ventilator support, longer duration of stay in the pediatric intensive care unit, more frequent association with electrolyte disturbances like hypokalemia and hypocalcemia and also shows higher incidence of sepsis than normomagnesemia.

References:

1. Limaye CS, Londhey VA, Nadkart MY & Borges NE. Hypomagnesemia in critically ill medical patients. Journal of association of physicians of India. 2011; (59): 19-22.
2. Maliakal P & Ledford A. Electrolyte and protein imbalance following anti-EGFR therapy in cancer patients: A comparative study. Experimental and therapeutic medicine. 2010; 1(2): 307-311.
3. Sekulic, A. D., Trpkovic, S. V., Pavlovic, A. P., Marinkovic, O. M., & Ilic, A. N.: Scoring systems in assessing survival of critically ill ICU patients. Medical science monitor: international medical journal of experimental and clinical research, 2015; 21: 2621.
4. Bhadoria P & Bhagwat AG. Severity scoring systems in paediatric intensive care units. Indian Journal of Anaesthesia. 2008; 52(5): 663-75.
5. Pollack Murray M1, Ruttimann UE and Getson PR. Pediatric Risk of Mortality score. Crit Care Med. 1988; 16(11):1110-1116.
6. Long Samantha and Andrea MP Romani. Role of Cellular Magnesium in Human Diseases. Austin journal of nutrition and food sciences. 2014; 2(10): 1051.
7. Das, Kumar, Arpan Bhattacharya Debasishghosh, and Milan Chakraborty. Prevalence of Hypomagnesemia and its Predictive Prognostic Value in Critically ill Medical Patients. IOSR Journal of Pharmacy. 2014; (4)1:1-5.
8. Soliman HM, Mercan D, Lobo SS, Mélot C, & Vincent JL. Development of ionized hypomagnesemia is associated with higher mortality rates. Critical care medicine. 2003; 31(4): 1082-1087.
9. Demircan, Fatih, Yasar Altun, and Faruk Kılınc: Hypomagnesemia in Internal Care Unit. International Journal of Basic and Clinical Studies. 2013; 1(1): 180-189.
10. Safavi M & Honarmand A. Admission hypomagnesemia--impact on mortality or morbidity in critically ill patients. Middle East journal of anesthesiology. 2007; 19(3): 645-660.
11. Kumar S, Honmode A, Jain S, & Bhagat V. Does magnesium matter in patients of Medical Intensive Care Unit: A study in rural Central India. Indian Journal of Critical Care Medicine. 2015; 19 (7): 379–383.
12. Chen, M., Sun, R., & Hu, B.: The influence of serum magnesium level on the prognosis of critically ill patients. Zhonghua Wei zhong Bing, ji jiu yi xue (= Chinese critical care medicine journal), 2015; 27(3): 213-217.
13. Saleem AF & Haque A. On admission hypomagnesemia in critically ill children: Risk factors and outcome. Indian journal of pediatrics. 2009; 76(12): 1227-1230.
14. Hulst, J. M., van Goudoever, J. B., Zimmermann, L. J., Tibboel, D., & Joosten, K. F.: The role of initial monitoring of routine biochemical nutritional markers in critically ill children. The Journal of nutritional biochemistry, 2006; 17(1): 57-62.
15. Oliveira Ana Beatriz FD, Dias OM, Mello MM, Araújo S, Dragosavac D, Nucci A. et al., Factors associated with increased mortality and prolonged length of stay in an adult intensive care unit. Revista Brasileira de terapia intensive [in Portuguese]. 2009; 22(3): 250-256.
16. Atkar CM and Gedam MV. Hypomagnesemia in Critically Ill Patients, Vidarbha Journal of Internal Medicine. 2016; 21(3): 60.
17. Zafar Mir S H, Wani JI, Karim R, Mir MM & Koul PA. Significance of serum magnesium levels in critically ill patients: International journal of applied basic and medical research. 2014; 4(1): 34-37.
18. Mousavi Seyed A J, Salimi S & Rezai M. Serum magnesium level impact on the outcome of patients admitted to the intensive care unit. Tanaffos journal. 2010; 9(4): 28-33.
19. Dabbagh OC, Aldawood AS, Arabi YM, Lone NA, Brits R & Pillay M. Magnesium supplementation and the potential association with mortality rates among critically ill non-cardiac patients. Saudi medical journal. 2006; 27(6): 821-825.
20. Huijgen, H. J., Soesan, M., Sanders, R., Mairuhu, W. M., Kesecioglu, J., & Sanders, G. T.: Magnesium levels in critically ill patients. American journal of clinical pathology, 2000; 114(5): 688-695.
21. Ñamendys-Silva, S. A., Correa-García, P., García-Guillén, F. J., Texcocano-Becerra, J., Colorado-Castillo, G., Meneses-García, A., &

Herrera-Gómez, A.: Hypomagnesaemia in critically ill patients with haematological malignancies. Nutricion hospitalaria, 2014; 30(1): 183-187.
22. Švagždienė M, Širvinskas E, Baranauskienė D & Adukauskienė D. Correlation of magnesium deficiency with C-reactive protein in elective cardiac surgery with cardiopulmonary bypass for ischemic heart disease. Medicina. 2015; 51(2), 100-106.
23. Kiran HS, Sriramachandrudu A, Murthy KS & Gowdappa HB. Serum Magnesium levels in critically ill patients–A Prospective Study. International Journal of Scientific Study. 2015; 3(7): 241-244.
24. Li Lin, Streja E, Rhee CM, Mehrotra R, Soohoo M, Brunelli SM. et al., Hypomagnesemia and mortality in incident hemodialysis patients. American Journal of Kidney Diseases. 2015; 66(6): 1047-1055.
25. Mutnuri, Sangeeta, Isaac Fernandez and Tina Kochar. Suppression of Parathyroid Hormone in a Patient with Severe Magnesium Depletion, Case reports in nephrology. 2016; 2016. Article ID 2608538.
26. Cojocaru IM, Tanasescu R, Iacob SA, & Iliescu IULIANA. Changes of magnesium serum levels in patients with acute ischemic stroke and acute infections. Rom J Intern Med. 2009; 47(2): 169-171.
27. Guerrero-Romero F & Rodriguez-Moran M. Relationship between serum magnesium levels and C-reactive protein concentration, in non-diabetic, non-hypertensive obese subjects. International journal of obesity. 2002; 26(4):469.
28. Fairley, J., Glassford, N. J., Zhang, L., & Bellomo, R.: Magnesium status and magnesium therapy in critically ill patients: a systematic review. Journal of critical care.2015, 30(6): 1349-1358.
29. Chattopadhyay, Jyotiprakas, and Morrell M. Avram. Serum magnesium concentration is a significant predictor of mortality in peritoneal dialysis patients. Advances in Peritoneal Dialysis.2014, vol.30.
30. Sari, A. P., Pitoyo, C., Aditianingsih, D., & Rumende, C.: Admission hypomagnesemia as a mortality predictor in medical critically ill patients. Critical Care. 2014, 18(1): P431.
31. Upala, S., Jaruvongvanich, V., Wijarnpreecha, K., & Sanguankeo, A. Hypomagnesemia and mortality in patients admitted to intensive care unit: a systematic review and meta-analysis. QJM. 2016, hcw048.

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