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ORIGINAL ARTICLE

High- and low-inpatients' serum magnesium levels are associated with in-hospital mortality in elderly patients: a neglected marker?

Giulia Lorenzoni[1] · Subhashisa Swain[1] · Corrado Lanera[1] · Mihaela Florin[2] · Ileana Baldi[1] · Sabino Iliceto[1] · Dario Gregori[1]

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Abstract

Background Altered serum magnesium (Mg) level in the human body has been hypothesized to have a role in the prediction of hospitalization and mortality; however, the reported outcomes are not conclusive.

Aims The present study aimed to analyze the relationship between serum Mg and in-hospital mortality (IHM) in patients admitted to the medical ward of two hospitals in the Veneto region (Italy).

Methods Patients > 18 years hospitalized in the medical wards of the hospitals of Vittorio Veneto and Conegliano, Italy (from January 12, 2011, through December 27, 2016) with at least one measurement of serum Mg were included in the study. A logistic regression model was used to assess the unadjusted and adjusted (by age, gender, Charlson Comorbidity index, discharge diagnosis' class) association of serum Mg and IHM.

Results In total 5024 patients were analyzed, corresponding to 6980 total admissions. The unadjusted analysis showed that IHM risk was significantly higher with 0.2 mg/dl incremental serum Mg level change from 2.4 mg/dl to 2.6, (OR 1.71 95% CI 1.55–1.89) and with 0.2 mg/dl change from serum Mg level of 1.4 mg/dl to 1.2 mg/dl, (OR 1.28 95% CI 1.17–1.40). Such results were confirmed at adjusted analysis.

Discussion Present findings have relevant implications for the clinical management of patients suffering from medical conditions, highlighting the need for analyzing Mg concentration carefully.

Conclusions Serum Mg levels seem to be a good predictor of IHM.

Keywords Mortality · Serum magnesium · Hospitalization · Elderly · Medical ward

Introduction

There is large evidence available on the effect of minerals such as potassium and sodium on human physiology and disease process [1]. In addition to that, recent researches are advancing and advocating the importance of magnesium (Mg) in various chronic diseases [2]. In the adult human body, Mg is commonly present in bones (≈ 60%), muscles (≈ 20%) and other soft tissues, and 1% of the total body Mg is available in extra cellular fluids. Mg, being one of the most commonly found element in human body, influences the physiological function of human body through enzymes, participation in cell metabolism process, metabolism of nutrients such as carbohydrates, proteins, fats, nucleic acids, electrophysiological and neuromuscular transmission and regulation of blood pressure and glucose levels [3, 4]. Growing evidence is available on wider involvement of Mg in physiological processes of the body which influences the functioning of the most of the systems ranging from renal, endocrine, and cardiac to central nervous system [5–7].

Similar to sodium (Na+) and potassium (K+), the change in the level of Mg in the human body has an impact on various physiological functioning. Studies have shown that hypomagnesemia, i.e., decreased level of Mg in serum (from the normal range) has a greater impact on cardio-vascular and renal system through blood pressure regulation [8], intra and extra cellular function [9], thrombosis [10],

✉ Dario Gregori
dario.gregori@unipd.it

[1] Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, Via Loredan, 18, 35131 Padua, Italy

[2] Medical Department, Vittorio Veneto Hospital, Vittorio Veneto, Italy

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and arrhythmia [11]. However, inconsistencies exist around the determination of thresholds for hypomagnesemia, which widely varies across the biological system impairment [12]. Most of the literature on Mg and health outcomes available has predicted the mortality among patients with renal insufficiency undergoing dialysis and have cardiac diseases [13, 14]. Review articles available on Mg and health outcomes have linked the increased level of this cation with increased mortality among heart-failure patients and better glucose level control among diabetic patients [15].

A growing number of studies are showing favorable evidence on using Mg level during hospitalization towards mortality rate. Studies from developed countries like the USA, Switzerland, and Italy have documented the positive association between serum hypermagnesemia with mortality outcome [16–19]. However, one prospective epidemiological study from the USA has reported that very low serum Mg concentrations were significantly associated with an increased risk of all-cause mortality [20]. Another study done on critically ill patients in India documented higher mortality, increased ventricular support, and increases complication among serum hypomagnesemia patients [21]. A systematic review on hypomagnesemia patients admitted to intensive care units has supported the evidence on the increased need for care support and mortality among these patients [22]. Corbi et al. [23] have conducted a study on elderly Italian cardiac patients, predicted the mortality with congestive heart disease to be higher among patients with hypermagnesemia because of increased use of laxatives and antacids.

The uncertain evidence on the impact of both low and high Mg levels on the prediction of hospitalization and mortality deserves further investigations. In addition to that, the presence of preexisting chronic conditions and drug use influences the serum Mg level, which affects the mortality prediction. Extending the research to study the impact of Mg level in other conditions such as cancer or neurological diseases in predicting the mortality outcome will be an addition to clinical decision-making system.

Considering such a framework, the aim of the present study was to analyze the relationship between serum Mg and in-hospital mortality (IHM) in patients admitted to medical ward of two hospitals in the Veneto region (Italy).

Materials and methods

Study design and patient population

Hospitalizations of patients > 18 years in the medical wards of the hospitals of Vittorio Veneto and Conegliano, Italy (from January 12, 2011, through December 27, 2016) were considered in the study. To be considered in the study, at least one measurement of serum Mg must be performed during the hospitalization.

De-identified hospital discharge records and laboratory data (serum Mg) were linked to each other. The exposure of interest was the first (baseline) serum Mg measurement (as mg/dl) performed during the hospital stay. For descriptive purposes, serum Mg levels were grouped in three categories, according to the literature [19, 24, 25] (≤ 1.6, $1.7–\leq 2.4$, > 2.4), whereas for all other purposes the Mg levels were considered on a continuous scale. The outcome of interest was IHM, which was identified from hospital discharge records.

To maximize the ascertainment of comorbidity, the Charlson index, as adapted by Romano et al. for use with administrative data [26] was computed.

To account for the patients' medical condition, the discharge diagnosis was grouped in classes using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The following classes were identified: neoplasms (ICD-9-CM codes 140-239), endocrine, nutritional and metabolic diseases, and immunity disorders (ICD-9-CM codes 240-279), diseases of the nervous system and sense organs (ICD-9-CM codes 320-389), diseases of the respiratory system (ICD-9-CM codes 460-519), diseases of the circulatory system (ICD-9-CM codes 390-459), and other diseases.

Statistical analysis

Continuous variables were reported as I quartile/median/III quartile, categorical variables as percentages (absolute number). Wilcoxon test was performed for continuous variables (i.e., age); the likelihood ratio Chi square test from the proportional odds model was performed for categorical ordered variables (i.e., Charlson index); and Pearson Chi square test was performed for categorical non-ordered variables (i.e., sex, death, and diagnosis groups) at the significance level of $p < 0.05$.

A logistic regression model was used to assess the unadjusted and adjusted (by age, gender, Charlson index, discharge diagnosis' class) association of serum Mg (considered on a continuous scale) and IHM. Linear tail-restricted cubic spline functions [27] with three knots, in correspondence with values chosen for identifying the cutoff values used in the descriptive analysis, were used to model the non-linear association of the serum Mg (considered on a continuous scale) with the IHM in both the unadjusted and adjusted models, and to model the non-linear association of the age with the IHM in the adjusted model. Potential different effect of Mg on IHM within each discharge diagnosis group was investigated adding an interaction term between Mg levels and discharge group. Huber–White method [28] was used to adjust the variance–covariance matrix of the models to

correct for heteroscedasticity and correlated responses from repeated hospitalizations of the same patient. Statistical analysis was performed using software R (ver. 3.5.2) [29], provided with package 'rms' [30], and 'medicalrisk' [31].

Results

The study included 6980 hospital admissions, with at least one serum Mg measurement, in the medical wards of the hospitals of Vittorio Veneto and Conegliano between 2011 and 2016. The hospital admissions account for 5024 patients because some patients had more than one hospitalization during the study period with at least one serum Mg measurement. Table 1 reports hospitalizations' characteristics stratified according to Mg levels of the first Mg measurement of each hospital admission (if more than one Mg measurement was performed during the same hospital stay). Table 2 reports patients' characteristics stratified according to the serum Mg levels of the first hospital admission (if more than one hospital admission was performed for the same patient). Significant differences in the age distribution and the proportion of in-hospital deaths were identified [patients in the group with the highest Mg concentration (> 2.4 mg/dl) were significantly older (p value 0.028) and presented a significantly higher (p value < 0.001) proportion of deaths]. It is worth pointing out that about a half of the hospitalizations in the low serum Mg category (≤ 1.6) were found to have very low serum Mg (≤ 1.4). Those hospitalizations were 1712 and they account for 1180 patients (59% females, median age 81 years old). The proportion of death in such group was 13% (157).

Table 3 reports hospitalizations' characteristics stratified according to the outcome of the hospitalization (resulting or not in the death of the patient).

The unadjusted analysis of the association between serum Mg and IHM (Fig. 1) showed that the mortality risk was significantly higher with 0.2 mg/dl incremental change (2.4–2.6, OR 1.71 95% CI 1.55–1.89). Conversely, a 0.2 decremental change in serum Mg (from 1.6 mg/dl down to 1.4 mg/dl) was found to be not significantly associated with IHM (OR 1.07 95% C.I. 1.00 – 1.13), but a further 0.2 mg/dl decremental change (from 1.4 mg/dl down to 1.2 mg/dl, corresponding to severe hypomagnesemia) was found to be in a significant direct association with IHM (OR 1.28 95% CI 1.17–1.40). At adjusted analysis

Table 1 Discharge diagnosis and Charlson index at hospital admissions (6980) according to serum Mg levels

	N	≤ 1.6 mg/dl (*N* = 3984)	> 1.6–2.4 mg/dl (*N* = 2956)	> 2.4 mg/dl (*N* = 40)	Combined (*N* = 6980)	*P* value
Charlson Index	6980	1 [0; 2]	1 [0; 2]	0 [0; 2]	1 [0; 2]	0.856
Discharge diagnosis	6980					<0.001
Diseases of the circulatory system		32% (1270)	32% (955)	15% (6)	32% (2231)	
Endocrine/nutritional/metabolic diseases and immunity disorders		2% (99)	2% (65)	0% (0)	2% (164)	
Diseases of the nervous system		7% (262)	8% (225)	5% (2)	7% (489)	
Neoplasms		10% (409)	9% (272)	2% (1)	10% (682)	
Diseases of the respiratory system		17% (675)	20% (591)	48% (19)	18% (1285)	
Other		32% (1269)	29% (848)	30% (12)	31% (2129)	

Data are percentage (absolute number) for categorical variables, and median (I quartile; III quartile) for continuous variables

Table 2 Description of sample characteristics (5024 patients) according to serum Mg levels

	≤ 1.6 mg/dl (*N* = 2839)	> 1.6–2.4 mg/dl (*N* = 2156)	> 2.4 mg/dl (*N* = 29)	Combined (*N* = 5024)	*P* value
Gender					0.002
Female	57% (1630)	53% (1132)	48% (14)	55% (2776)	
Male	43% (1209)	47% (1024)	52% (15)	45% (2248)	
Death					< 0.001
No	90% (2559)	87% (1866)	55% (16)	88% (4441)	
Yes	10% (280)	13% (290)	45% (13)	12% (583)	
Age	81.6 [73.0; 87.5]	81.8 [72.6; 88.0]	85.0 [80.8; 89.3]	81.7 [72.9; 87.7]	0.028

Data are percentage (absolute number) for categorical variables, and median (I quartile; III quartile) for continuous variables

Table 3 Discharge diagnoses and serum Mg levels according to the outcome of the hospital admission (hospitalizations resulting in the death of the patient vs those not resulting in the death of the patient)

	Hospitalizations not resulting in the death of the patient ($N=6071$)	Hospitalizations resulting in the death of the patient ($N=909$)	Combined ($N=6980$)	P value
Discharge diagnosis				< 0.001
Diseases of the circulatory system	33% (2003)	25% (228)	32% (2231)	
Endocrine/nutritional/metabolic diseases and immunity disorders	3% (157)	1% (7)	2% (164)	
Diseases of the nervous system	8% (482)	1% (7)	7% (489)	
Neoplasms	9% (527)	17% (155)	10% (682)	
Diseases of the respiratory system	16% (986)	33% (299)	18% (1285)	
Other	32% (1916)	23% (213)	31% (2129)	
Serum magnesium				< 0.001
≤ 1.6 mg/dl	58% (3549)	48% (435)	57% (3984)	
> 1.6–2.4 mg/dl	41% (2502)	50% (454)	42% (2956)	
> 2.4 mg/dl	0% (20)	2% (20)	1% (40)	

Data are percentage (absolute number) for categorical variables, and median [I quartile; III quartile] for continuous variables

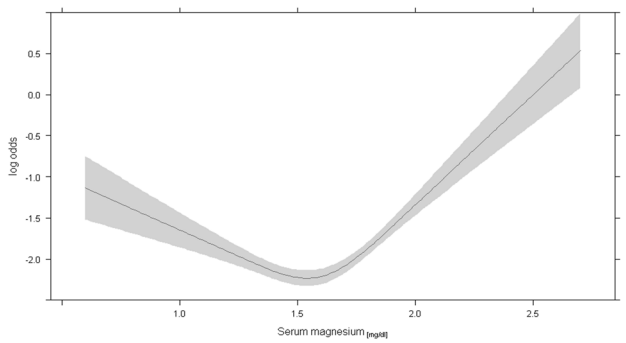

Fig. 1 Unadjusted association of serum Mg and in-hospital mortality. Unadjusted OR of death 1.07 (95% CI 1.00–1.13) in the range from 1.6 mg/dl down to 1.4 mg/dl, 1.28 (95% CI 1.17–1.40) in the range from 1.4 mg/dl down to 1.2 mg/dl, and 1.71 (95% CI 1.55–1.89) in the range from 2.4 mg/dl up to 2.6 mg/dl (P value for non-linearity < 0.0001)

(Table 4), subjects with 0.2 mg/dl incremental change of serum Mg (from 2.4 mg/dl up to 2.6 mg/dl), were found to have a significantly higher risk of death for all discharge diagnoses classes except for the diseases of the nervous system (OR 1.648 95% CI 1.386–1.958 diseases of the circulatory system; OR 2.207 95% CI 1.223–3.985 endocrine/nutritional/metabolic diseases and immunity disorders; OR 1.964 95% CI 1.521–2.536 neoplasms; OR 1.55 95% CI 1.301–1.846 diseases of the respiratory system). Patients with neoplasms were found to have a significantly higher risk of death also with 0.2 decremental change of serum Mg (OR 1.188 95% CI 1–1.412 from 1.6 mg/dl down to 1.4 mg/dl and OR 1.539 95% CI 1.194–1.982 from 1.4 mg/dl down to 1.2).

Discussion

This work aimed at assessing the relationship between serum Mg levels and all-cause IHM in patients admitted to the medical ward of two hospitals in the Veneto region (Italy).

Interestingly, to our knowledge, this is the first study showing that both very low and high serum Mg were independently associated with all-cause mortality in medical patients. As the general medical ward receives a wide variety of patients representing heterogeneous medical conditions, it was possible to assess both low and high Mg levels and their relationship with IHM. This is because it is well known that hypermagnesemia is markedly less frequent compared to hypomagnesemia [6]. Indeed, and also in our sample, patients were more likely to show low levels of Mg concentrations instead of high ones.

Evidence about the association between Mg levels and mortality risk is growing rapidly, even though the pathophysiologic mechanism underlying such association is not yet well understood. Various evidence have mentioned the possible physiological impact of Mg level change such as decreased immunity [32] increased inflammation [20, 33] and cardiovascular disease [34]. Little evidence is available on high Mg and its role in physiological and pathological changes in the body, which needs further investigations.

The results of both unadjusted and adjusted analyses showed that both very low (0.2 decremental change in serum Mg from 1.4 to 1.2 corresponding to severe hypomagnesemia) and high Mg levels are an independent predictor of all-cause mortality. This is consistent with several studies that have already shown a significant association between low serum Mg and all-cause mortality both in general population [20] and in patients suffering from acute or chronic conditions [35–38]. The studies on

Table 4 Multivariable analysis of the association between Mg concentrations and mortality

		Odds ratio	Low 95% CI	High 95% CI	*P* value
Age	73 vs 87	1.844	1.636	2.079	< 0.001
Gender	Male vs female	1.113	0.956	1.294	0.122
Charlson Index	0 vs 2	1.177	1.051	1.318	0.009
Diseases of the circulatory system: Mg concentration (mg/dl)	1.4 vs 1.2	1.191	0.992	1.43	0.058
	1.6 vs 1.4	1.017	0.895	1.157	0.415
	2.4 vs 2.6	1.648	1.386	1.958	< 0.001
Endocrine/nutritional/metabolic diseases and immunity disorders: Mg concentration (mg/dl)	1.4 vs 1.2	0.793	0.31	2.028	0.658
	1.6 vs 1.4	0.696	0.346	1.398	0.803
	2.4 vs 2.6	2.207	1.223	3.985	0.014
Diseases of the nervous system: Mg concentration (mg/dl)	1.4 vs 1.2	1.232	0.353	4.292	0.392
	1.6 vs 1.4	1.113	0.433	2.858	0.426
	2.4 vs 2.6	1.253	0.988	1.589	0.059
Neoplasms: Mg concentration (mg/dl)	1.4 vs 1.2	1.539	1.194	1.982	0.003
	1.6 vs 1.4	1.188	1	1.412	0.05
	2.4 vs 2.6	1.964	1.521	2.536	< 0.001
Diseases of the respiratory system: Mg concentration (mg/dl)	1.4 vs 1.2	1.185	0.983	1.429	0.068
	1.6 vs 1.4	1.028	0.904	1.17	0.362
	2.4 vs 2.6	1.55	1.301	1.846	< 0.001
Other diagnoses: Mg concentration (mg/dl)	1.4 vs 1.2	1.304	1.105	1.541	0.004
	1.6 vs 1.4	1.083	0.966	1.213	0.125
	2.4 vs 2.6	1.703	1.43	2.028	< 0.001

Model with Mg levels modeled as a continuous variable via a restricted cubic spline, with 3 knots. Adjusting factors are age, gender, Charlson index and discharge diagnosis, and an interaction term between discharge diagnosis and Mg levels. Data of interaction are presented as odds ratios of the effect of Mg in each diagnosis subgroup. Odds ratios are reported as "*A* vs *B*" value variations for each factor, where *A* is the reference value and *B* is the target value

patients with chronic or acute diseases focused mainly on the association between low Mg concentrations and mortality in patients suffering from kidney diseases, since low serum Mg is related generally to the use of diuretics. The added value of the present study is that, unlike the previous research works, it did not concentrate only on a specific cluster of patients with homogenous characteristics (i.e., patients undergoing hemodialysis for kidney disease), allowing for a broader understanding of the phenomenon of mortality associated with serum concentrations in patients with both acute and chronic diseases.

Differently from hypomagnesemia, which has been extensively studied, the role of hypermagnesemia in affecting mortality risk has been studied less frequently. Two recent studies [16, 19] conducted on critical patients showed a higher mortality risk for patients with serum Mg > 2.4 mg/dl or 2.5 mg/dl, consistently with the results of the present investigation. Anyway, the results of the present study for what concerns hypermagnesemia should be taken with caution given the small sample of patients with serum Mg levels > 2.4 mg/dl.

Study limitations

The main study limitation is represented by the non-availability of death causes. A poor agreement between discharge diagnosis and causes reported in death certificates has been shown [39]. However, this has been ascribed mainly to a wrong classification of deaths' causes (e.g., overreporting of cardiac causes) and it has been reported that the agreement between such two sources of data decreases after the discharge [40]. Therefore, according to such assumptions, the discharge diagnosis might be considered a good proxy of the cause of death for in-hospital mortality.

In addition to that, the present analysis did not account for a comprehensive geriatric assessment (CGA) since administrative data used did not allow for the assessment of geriatric syndromes.

Not least, the Charlson index was computed using hospital discharge records, according to Romano et al. procedure [26]. In the last 30 years, several studies have explored the validity of administrative data (including hospital discharge records) for computing the Charlson index. The use

of administrative data should be considered carefully [41]. In addition to that, in the present study, only two discharge diagnosis fields were available for each hospital discharge record, leading to a restricted ascertainment of the comorbidities for computing the Charlson index. This is probably one of the main reasons why the Charlson index was found to be lower than expected from the clinical point of view for the most severe patients. Anyway, despite this limitation, the Charlson index was found to be significantly directly associated with IHM, and this is consistent with previous studies that used administrative data to compute the Charlson index [42].

Conclusion

Present findings might have clinical implications in medical in-patients, highlighting the association of serum Mg levels at the time of hospital admission with in-hospital mortality. However, we cannot rule out that, although serum Mg levels may be implicated in these deaths, it might be that Mg levels are a surrogate of diseases and therapies which may have contributed to the death. Further studies are needed to better characterize the association between serum Mg levels and IHM.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals Since the study was retrospective and used only de-identified data, the ethical approval was not needed.

Informed consent Individual informed consent was not needed since the study was retrospective and only de-identified data were shared for the study.

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