ORIGINAL ARTICLE

Post-kidney transplant serum magnesium exhibits a U-shaped association with subsequent mortality: an observational cohort study

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SUMMARY

Hypomagnesemia is common in kidney transplant recipients (KTRs). We sought to explore the relationship between Mg and outcomes in KTRs, which may be associated with mortality and thus may be a potential intervention target to improve outcomes. We followed KTRs performed between 01/2000 and 6/2016 at a large US transplant center from 6 months post-transplant to graft failure, death, or loss to follow-up. Using Mg as a time-dependent variable, associations between Mg and outcomes any time after 6 months post-transplant were evaluated. 3680 KTRs with 50 413 Mg measurements met inclusion criteria. 657 deaths occurred over a median follow-up of 5.1 years. Compared to Mg of 1.5–1.8 mg/dl, both lower (HR 1.17, 95% confidence interval (CI): 1.07–1.28) and higher (HR 1.16, 95% CI: 1.09–1.23) Mg levels were associated with greater risk of mortality. Similar U-shaped associations were observed for Mg and cardiovascular disease-related mortality (HR for Mg ≤1.5 mg/dl: 1.31; CI: 1.03–1.68) and infection-related mortality (HR for Mg ≤1.5 mg/dl: 1.28; CI: 1.09–1.51), although relationships for Mg >1.8 mg/dl were not statistically significant. Mg exhibits a U-shaped association with mortality in KTRs, with levels between 1.5 and 1.8 mg/dl associated with the lowest risk.

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Key words
kidney transplantation, magnesium, mortality, outcomes

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Introduction

Magnesium (Mg) is the second most abundant intracellular cation. It serves as a cofactor for more than 600 enzymatic reactions and thereby plays a significant role in essentially every intracellular biologic process [1]. It is important for cardiovascular functions, including vascular tone and heart rhythm, and for immunological functions, including immunoglobulin synthesis, C3 convertase activity, and immune cell binding and adherence [2,3].

Several studies have shown an association between hypomagnesemia and high risk of all-cause, cardiovascular disease (CVD)-related, and non-CVD-related mortality in chronic kidney disease (CKD) and end-stage kidney disease (ESKD) populations [4–6]. Given the wide-ranging biologic functions that depend on Mg, a multitude of factors likely underlie these associations. One of those factors which may explain the higher CVD-related mortality with hypomagnesemia is the anti-atherosclerotic effect of Mg [7,8]. Hypomagnesemia is a

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common finding in kidney transplant recipients (KTRs.) This is in part due to the widespread use of calcineurin inhibitors (CNI), which have been the mainstay immunosuppressive therapy for the past three decades [9]. The mechanism of CNI-induced hypomagnesemia is hypothesized to be the downregulation of the putative Mg channel, transient receptor potential melastatin 6, in the distal convoluted tubule [10–13]. Several other factors likely contribute to hypomagnesemia in KTRs, including low dietary Mg intake, decreased intestinal absorption due to diarrhea or proton pump inhibitor (PPI) use, and increased urinary losses as a result of diuretics [14–17].

In KTRs, low Mg level is a risk factor for post-transplant diabetes mellitus [18–20] and increased vascular stiffness [21]. However, data on the association between serum Mg level and mortality are lacking. Studying the association between Mg levels and adverse outcomes and identifying optimal serum levels is important, as it can help identify a predictor/risk factor for subsequent mortality and, more importantly, provide a potential target for intervention that ultimately may help improve outcomes for these patients.

In this study, we explored the association between serum Mg levels and all-cause and cause-specific mortality using a large single-center database.

Materials and methods

Study population

KTRs were selected from the Wisconsin Allograft Recipient Database (WisARD), which was established at the University of Wisconsin in 1984. We included all adult kidney-alone transplant recipients between January 1, 2000, and June 30, 2016, who were alive with a functioning allograft at six months after transplantation and had at least one serum Mg level available after six months post-transplant. Recipients younger than 18 years of age at the time of transplant and recipients of multi-organ transplants were excluded. The six-month time point was selected as by this time point, patients are likely to have reached stable kidney allograft function and be on stable immunosuppressive, in particular CNI, and antihypertensive regimens.

Exposure

The exposure of interest was serum Mg level after 6 months post-transplantation. Due to potential fluctuations in Mg levels observed during hospitalizations, only Mg levels obtained in the outpatient setting were included in our analyses. Baseline Mg was defined as the mean of the Mg levels available from the outpatient setting between 6 and 18 months post-transplantation.

Outcomes

The primary outcome in our study was all-cause mortality. Secondary outcomes included cause-specific mortality, namely CVD-related mortality and infection-related mortality. Deaths were categorized based on the United Network for Organ Sharing primary cause of death.

Covariates

Data were collected on baseline demographic and clinical characteristics of the recipients, induction and maintenance immunosuppression regimens used, and post-transplant complications including delayed graft function and rejection in the first 6 months. Race was categorized as White, Black, or other. The number of human leukocyte antigen (HLA) mismatches at HLA-A, HLA-B, and HLA-DRB1 loci out of a total of 6 was collected and categorized as 0–2, 3–4, or 5–6. The year of transplant was also included in order to be able to adjust for any era effect. Other variables included smoking status, body mass index (BMI), cause of ESKD, living vs. deceased donor transplant, history of prior transplants, pre-emptive vs. requiring dialysis prior to transplant, and in the case of the latter, duration of dialysis, induction immunosuppression, and maintenance immunosuppression. Data on whether recipients had a diagnosis of ischemic heart disease, arrhythmic heart disease, or heart failure prior to 6 months post-transplantation were also included. Cardiovascular disease was defined as coronary heart disease, arrhythmia, heart failure, or cerebrovascular disease before 6 months post-transplantation. The estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [22]. Baseline eGFR and CNI levels were assessed as the mean of all values obtained between 6 and 18 months post-transplantation. Lastly, data on post-transplant PPI and Mg supplementation use between 6 and 18 months post-transplantation were also included. In our data, about 20% of participants were missing smoking information. We used multiple imputation to generate 20 datasets using a conditional specification approach.

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Statistical analyses

Differences in baseline characteristics were compared by Student's t-tests or chi-square tests, as appropriate. Cox proportional hazards regression models were used to analyze the relationship between serum Mg and all-cause mortality and cause-specific mortality. Patients were followed from six months after transplantation until death, graft failure, loss to follow-up, or June 30, 2016. Proportional hazard assumption was tested by checking the Schoenfeld's partial residuals, and the assumption was satisfied.

Two sets of analyses were conducted. In our primary analysis, association between Mg and outcomes any time after 6 months post-transplant was evaluated. To appropriately account for changes in Mg level overtime, serum Mg level was treated as time-dependent exposure. The model updated the serum Mg level when a new Mg measurement became available. We used robust standard error to account for clustered Mg measurement with each patient. Serum Mg level was evaluated as a continuous variable and as a categorical variable (Mg $\leq$1.5 mg/dl, 1.5 mg/dl < Mg $\leq$1.8 mg/dl, and Mg > 1.8 mg/dl). Of note, these categories were established post hoc after observing the association between Mg level as a continuous variable and risk of all-cause mortality. Our secondary analysis assessed the association between the mean Mg level between 6 and 18 months post-transplant and risk of mortality any time after 18 months post-transplant. Similar analyses as above were performed using Mg level as a continuous and as a categorical variable, respectively.

In multivariable adjusted models, the following covariates were adjusted: (i) recipient factors including age at transplantation, sex, race, cause of ESKD, BMI at the time of transplant, prior transplant history, history of ischemic heart disease, history of arrhythmias, and history of heart failure before 6 months post-transplantation; (ii) transplantation-related factors including live donor transplantation, induction immunosuppression, maintenance immunosuppression, and transplantation year; and (iii) post-transplantation factors including mean eGFR and mean tacrolimus/cyclosporine levels in the baseline period. We did not adjust for diabetes because as expected, diabetes was highly correlated with cause of ESKD and collinearity between the two variables was observed in the regression models.

In sensitivity analyses, we stratified the analysis of Mg level and all-cause mortality by baseline eGFR level (<45 vs. $\geq$45 ml/min/1.73m^2). In addition, we adjusted for eGFR as a time-dependent covariate, that is, the eGFR was updated whenever there was a new eGFR available at the time of Mg measurement. We further assessed the association between median Mg level during baseline period and risk of mortality.

A statistically significant difference was defined by a two-sided p-value less than 0.05. All analyses were performed using R [23] (www.R-project.org/).

This study was approved by the Health Sciences Institutional Review Board at the University of Wisconsin. The Declaration of Helsinki was adhered to. Protected health information was deidentified, and informed consent was therefore waived for this study. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism."

Results

Subject population

Of the 4,376 recipients who received transplantation in the study period, 3,680 (84.1%) kidney transplant recipients were alive with a functioning graft at 6 months post-transplant and had at least 1 Mg measurement available (Fig. 1); these were included in our primary analysis using Mg as a time-dependent variable. Median (IQR) follow-up was 5.1 years (2.3, 5.8). Of these, 3327 recipients were alive with a functioning graft at 18 months post-transplant (Figure S1); these met eligibility criteria for our secondary analysis.

Baseline characteristics

Mean recipient age at the time of transplant was 49.5 years, 59.9% were men, and 83.2% were White (Table 1). Patients were categorized into three groups based on the mean serum Mg level in the baseline period, that is, between 6 and 18 months post-transplantation: $\leq$1.5 mg/dl (10.4%), 1.5–1.8 mg/dl (43.1%), and >1.8 mg/dl (46.5%). Patients in the lowest serum Mg level group were younger, less likely to be male and have diabetes as cause of ESKD, more likely to receive transplantation in more recent years, more likely to receive basiliximab as induction immunosuppression, and receive tacrolimus-based maintenance immunosuppression. Additionally, they were less likely to have delayed graft function or acute rejection within 6 months after transplantation. In addition, they had higher eGFR and higher CNI levels. Interestingly, 66.3%

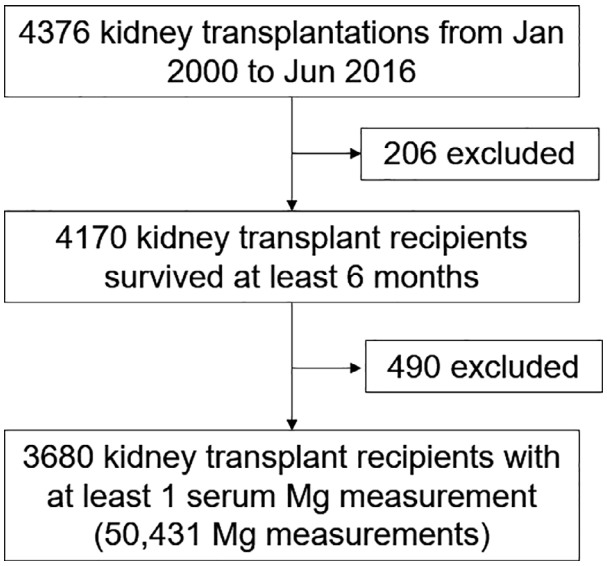

Figure 1 Inclusion criteria for the primary analysis using Mg as a time-varying variable. Adult kidney-only transplant recipients were included if they survived at least six months and if they had at least one serum Mg measurement.

were on PPI and 44.4% were on oral Mg supplementation. No significant difference in PPI use was observed in patients with different Mg level. As expected, patients in the lowest Mg category were more likely to be on oral Mg supplementation. There were no significant differences in the race distribution, BMI at the time of transplant, rates of pre-emptive transplantation, or duration of dialysis.

Primary analyses using serum Mg level as a time-dependent exposure

The total number of Mg measurements available was 50,431; median (interquartile range (IQR)) per recipient was 10 (5, 16). The median interval between Mg measurements was 184 (45, 219) days.

In our cohort, there were 657 deaths any time after 6 months post-transplant, yielding a mortality of 17.8%. Using serum Mg level as a continuous variable, a U-shaped curve was observed for all-cause mortality in both the unadjusted (Fig. 2a) and the adjusted (Fig. 2b) models. Serum Mg of 1.5–1.8 mg/dl was associated with the lowest incidence of all-cause mortality in both the unadjusted and the adjusted analyses. Using serum Mg level as a categorical variable, with Mg of 1.5–1.8 mg/dl as the reference range, Mg ≤1.5 mg/dl was associated with 17% higher risk of death (hazard ratio (HR): 1.17 (95% confidence interval (95% CI: 1.07–1.28))) and Mg >1.8 mg/dl was associated with a 16% higher risk of death (HR 1.16 (95% CI: 1.09–1.23; Table 2)).

Similar U-shaped curves were observed for serum Mg level and CVD-related mortality ($n = 129$) and infection-related mortality ($n = 131$) in the unadjusted and the adjusted analyses (Figs 3a,b and 4a,b, respectively), though lower serum Mg levels appeared to confer higher risk in our adjusted models. Serum Mg ≤1.5 mg/dl was associated with a 31% higher risk of CVD-related mortality (HR 1.31 (95% CI: 1.03–1.68)) and a 28% higher risk of infection-related mortality (HR 1.28 (95% CI: 1.09–1.51)).

Secondary analyses using baseline serum Mg level

In our secondary analyses, we evaluated the relationship between mean serum Mg between 6 and 18 months after transplantation and subsequent risk of mortality. Among the 3327 KTRs who met inclusion criteria (Figure S1), there were 624 deaths yielding a mortality of 18.8%. Using Mg as a continuous variable, U-shaped associations were observed in both the unadjusted and the adjusted models (Figure S2A,B). Compared to mean Mg level of 1.5–1.8 mg/dl, HR for Mg <1.5 mg/ml was 1.04 (95% CI: 0.74–1.33) and for Mg >1.8 mg/dl was 1.41 (95% CI: 1.18–1.69) (Table S1).

A relatively low number of CVD-related ($n = 53$) and infection-related ($n = 61$) mortality events were observed. The relationships between Mg and CVD-related mortality (Figure S3A,B) and Mg and infection-related mortality (Figure S4A,B) were less obvious. Compared to mean Mg level of 1.5–1.8 mg/dl, HRs for CVD-related mortality with Mg <1.5 mg/ml and Mg >1.8 mg/dl were 1.13 (95% CI: 0.55–2.29) and 1.13 (95% CI: 0.75–1.70), respectively, and for infection-related mortality with Mg <1.5 mg/ml and Mg >1.8 mg/dl were 1.19 (95% CI: 0.63–2.39) and 1.31 (95% CI: 1.03–1.96), respectively.

Sensitivity analyses

We conducted the analyses of Mg as a time-dependent variable and all-cause mortality stratified by eGFR (<45 vs. ≥45 ml/min/1.73 m^2) (Figure S5). The U-shaped relationship was maintained among kidney transplant recipients with eGFR≥45 ml/min/1.73m^2. Among those with eGFR<45 ml/min/1.73m^2, higher Mg level was associated with higher risk of mortality; however, the relationship between low Mg level and mortality was not significant. Additionally, the association between Mg and mortality attenuated but remained U-shaped after adjusting for eGFR as time-dependent covariate (Figure S6). The association between median Mg level

Table 1. Baseline characteristics by serum Mg group.

	Total	Mg ≤1.5 mg/dl *n* = 347	1.5 mg/dl< Mg ≤1.8 mg/dl *n* = 1433	Mg >1.8 mg/dl *n* = 1547	*P*
Mean Mg level during baseline period (mean (SD))	1.83 (0.29)	1.43 (0.09)	1.69 (0.08)	2.06 (0.26)	<0.001
Number of Mg measurements (median [IQR])	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	<0.69
Age at transplant (years) (mean (SD))	49.54 (14.31)	47.68 (14.55)	49.05 (14.17)	50.42 (14.34)	0.001
Male (%)	1992 (59.9)	182 (52.4)	876 (61.1)	934 (60.4)	0.011
Race (%)					0.125
White	2768 (83.2)	275 (79.3)	1184 (82.6)	1309 (84.6)	
Black	287 (8.6)	39 (11.2)	123 (8.6)	125 (8.1)	
Other	272 (8.2)	33 (9.5)	126 (8.8)	113 (7.3)	
BMI at transplant (kg/m2) (mean (SD))	27.47 (5.43)	28.04 (5.91)	27.45 (5.42)	27.36 (5.31)	0.111
Cause of ESKD (%)					<0.001
Diabetic nephropathy	799 (24.0)	55 (15.9)	311 (21.7)	433 (28.0)	
Glomerulonephritis	833 (25.0)	89 (25.6)	355 (24.8)	389 (25.1)	
Hypertension	352 (10.6)	44 (12.7)	157 (11.0)	151 (9.8)	
Polycystic kidney disease	449 (13.5)	57 (16.4)	202 (14.1)	190 (12.3)	
Other	894 (26.9)	102 (29.4)	408 (28.5)	384 (24.8)	
Pre-emptive transplant (%)	896 (27.0)	100 (28.9)	404 (28.3)	392 (25.4)	0.143
Pretransplant dialysis duration, months (median [IQR])	12.00 [0.00, 31.00]	12.00 [0.00, 28.75]	12.00 [0.00, 30.00]	13.00 [0.00, 32.00]	0.214
Transplant year (median [IQR])	2007.00 [2003.00, 2011.00]	2010.00 [2004.50, 2013.00]	2008.00 [2004.00, 2011.00]	2006.00 [2003.00, 2009.00]	<0.001
Prior transplant (%)	607 (18.2)	64 (18.4)	244 (17.0)	299 (19.3)	0.266
HLA antigen mismatch (%)					0.106
1–2	852 (25.6)	71 (20.5)	360 (25.1)	421 (27.2)	
3–4	1350 (40.6)	144 (41.6)	590 (41.2)	616 (39.8)	
5–6	1124 (33.8)	131 (37.9)	483 (33.7)	510 (33.0)	
Induction immunosuppression (%)					<0.001
Basiliximab	1905 (57.3)	222 (64.0)	864 (60.3)	819 (52.9)	
Alemtuzumab	657 (19.7)	41 (11.8)	232 (16.2)	384 (24.8)	
Thymoglobulin	604 (18.2)	70 (20.2)	264 (18.4)	270 (17.5)	
Other	161 (4.8)	14 (4.0)	73 (5.1)	74 (4.8)	
Maintenance immunosuppression (%)					
Tacrolimus	2189 (65.8)	286 (82.4)	1042 (72.7)	861 (55.7)	<0.001
Cyclosporine	859 (25.8)	53 (15.3)	326 (22.7)	480 (31.0)	<0.001
Belatacept	30 (0.9)	0 (0)	2 (0.1)	28 (1.8)	<0.001
Azathioprine	11 (0.33)	3 (0.9)	3 (0.2)	5 (0.3)	0.17
Mycophenolate	3209 (96.4)	337 (97.1)	1396 (97.4)	1476 (95.4)	0.11
Sirolimus/Everolimus	162 (4.9%)	10 (2.9)	45 (3.1)	107 (6.9)	<0.001
History of diabetes mellitus (%)	902 (27.1)	62 (17.9)	360 (25.1)	480 (31.0)	<0.001
Smoking status (%)					0.972
Never	1682 (58.3)	187 (57.4)	743 (57.9)	752 (59.0)	
Former	998 (34.6)	115 (35.3)	448 (34.9)	435 (34.1)	
Current	203 (7.0)	24 (7.4)	92 (7.2)	87 (6.8)	
Living donor (%)	1413 (42.5)	135 (38.9)	615 (42.9)	663 (42.9)	0.365
Delayed function (%)	520 (15.6)	45 (13.0)	202 (14.1)	273 (17.6)	0.01
Acute rejection (%)	610 (18.3)	39 (11.2)	240 (16.7)	331 (21.4)	<0.001
eGFR (ml/min/1.73 m^2) (mean (SD))*	59.86 (18.73)	65.41 (20.89)	61.75 (19.20)	56.78 (17.17)	<0.001

Table 1. Continued.

	Total	Mg ≤1.5 mg/dl *n* = 347	1.5 mg/dl< Mg ≤1.8 mg/dl *n* = 1433	Mg >1.8 mg/dl *n* = 1547	*P*
CNI level ≥ 75th percentile (%)*	782 (23.5)	120 (34.6)	401 (28.7)	261 (19.1)	<0.001
Diagnosis of ischemic heart disease before 6 m post-transplant (%)	1062 (31.9)	106 (30.5)	462 (32.2)	494 (31.9)	0.832
Diagnosis of arrhythmic heart disease before 6 m post-transplant (%)	286 (8.6)	24 (6.9)	107 (7.5)	155 (10.0)	0.023
Diagnosis of heart failure before 6 m post-transplant (%)	419 (12.6)	40 (11.5)	177 (12.4)	202 (13.1)	0.692
Proton pump inhibitor use (%)*	2271 (68.3)	230 (66.3)	950 (66.3)	1091 (70.5)	0.033
Mg supplementation (%)*	954 (28.7)	154 (44.4)	449 (31.3)	351 (22.7)	<0.001
Diuretic use (%)	1005 (30.2)	90 (25.9)	374 (26.1)	601 (38.8)	<0.001

*Data on eGFR and CNI, proton pump inhibitor and Mg supplementation were obtained from the baseline period, that is, from 6 to 18 months after transplantation.

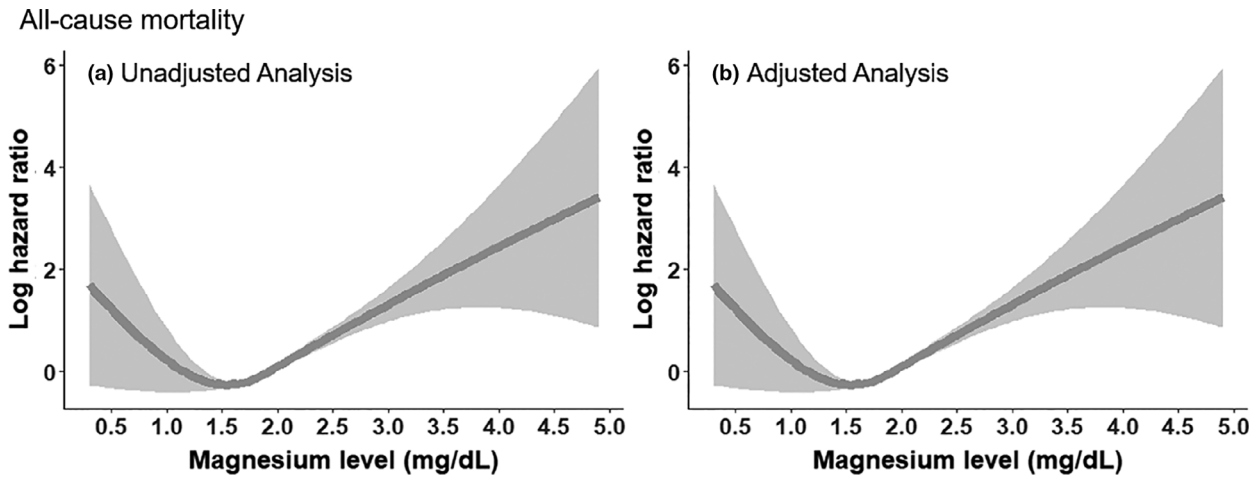

Figure 2 Relationship between serum Mg as a continuous variable and all-cause mortality for the unadjusted (a) and adjusted (b) analyses. The relationship is U-shaped, with levels between 1.5 and 1.8 mg/dl associated with the lowest mortality risk.

during the baseline period and mortality was similar compared with results in primary analyses (Figure S7). We also assessed the association between number of Mg measurement and risk of all-cause mortality and did not observe a significant association (HR 0.99, 95% CI: 0.96–1.02).

Discussion

Renal function is a key determinant in Mg homeostasis, and recently, Mg has drawn close attention in CKD and ESKD patients. KTRs represent a unique subset of this population. Several unique factors including increased urinary losses from CNI and diuretic use, and reduced GI absorption related to oral intake, PPI use, and diarrhea contribute to the hypomagnesemic state. Our study provides new insights into the association between serum Mg level and mortality in this population. Using a large database on adult kidney-only transplant recipients followed at a single center, we found a U-shaped association between serum Mg level and all-cause mortality, with a level between 1.5 and 1.8 mg/dl associated

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Table 2. Serum Mg as a categorical variable.

All-cause mortality	Death	Unadjusted HR	Adjusted HR
Mg ≤ 1.5 (*n* = 5806)	73 (1.3)	0.99 (0.91, 1.08)	1.17 (1.07, 1.28)
1.5 < Mg ≤ 1.8 (*n* = 13 401)	211 (1.6)	1.0 (Ref)	1.0 (Ref)
Mg > 1.8 (*n* = 16 495)	373 (2.3)	1.48 (1.40,1.56)	1.16 (1.09, 1.23)
CVD-related mortality			
Mg ≤ 1.5 (*n* = 5806)	9 (0.2)	0.98 (0.77, 1.24)	1.31 (1.03, 1.68)
1.5 < Mg ≤ 1.8 (*n* = 13 401)	42 (0.3)	1.0 (Ref)	1.0 (Ref)
Mg > 1.8 (*n* = 16 495)	78 (0.5)	1.51 (1.31, 1.76)	1.09 (0.92, 1.29)
Infection-related mortality			
Mg ≤ 1.5 (*n* = 5806)	16 (0.3)	1.11 (0.95, 1.30)	1.28 (1.09, 1.51)
1.5 < Mg ≤ 1.8 (*n* = 13 401)	39 (0.3)	1.0 (Ref)	1.0 (Ref)
Mg > 1.8 (*n* = 16 495)	76 (0.5)	1.32 (1.18, 1.47)	1.00 (0.89, 1.13)

Adjustments were made for age, sex, race, cause of ESKD, body mass index (BMI) at the time of transplant, prior transplant history, history of ischemic heart disease, history of arrhythmias, and history of heart failure before 6 months post-transplantation; living vs. deceased donor transplantation, induction immunosuppression (basiliximab vs. alemtuzumab vs. thymoglobulin vs. other), maintenance immunosuppression (tacrolimus vs. cyclosporine vs. other), and transplantation year; and mean eGFR and mean tacrolimus/cyclosporine levels in the baseline period.

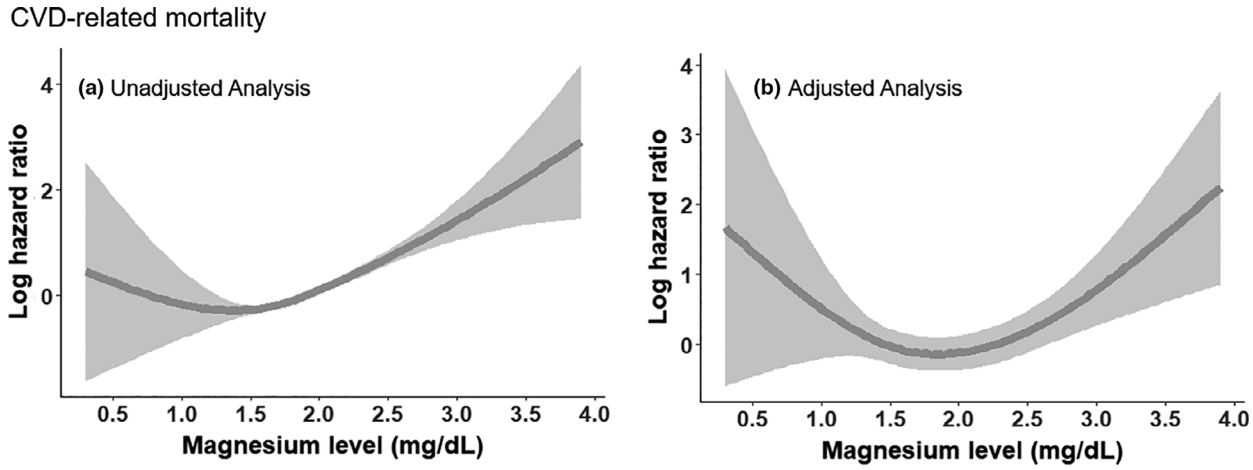

Figure 3 Relationship between serum Mg as a continuous variable and cardiovascular disease-related mortality for the unadjusted (a) and adjusted (b) analyses.

with the lowest risk of mortality. Additionally, similar U-shaped associations were noted between serum Mg levels and CVD-related mortality, with a 31% increase in risk of CVD-related death associated with a level less than 1.5 mg/dl, and between Mg level and infection-related mortality, with a 28% increase in risk of infection-related death with a level less than 1.5 mg/dl.

While the association between low Mg level and worse outcomes is not surprising, a notable observation was that the level 1.5–1.8 mg/dl overlaps with the lower end of the range defined as normal at our institution, which is 1.6–2.6 mg/dl, and an uptrend in mortality risk was observed beyond 1.8 mg/dl. Several prior studies in other disease states have documented U-shaped associations between Mg and outcomes, where the nadir coincides with low-normal values. A study of over 10 000 patients with acute myocardial infarction showed U-shaped associations between Mg and in-hospital mortality and malignant arrhythmias. The lowest risk of adverse events was seen at Mg levels of 1.7–1.9 mg/dl [24]. This study argued against the common practice in acute myocardial infarction to maintain Mg levels ≥2 mg/dl. A study by Cheungpasitporn et al. evaluated the risk of acute kidney injury in 9241 hospitalized patients and found that admission serum Mg between 1.7 and 2.1 mg/dl was associated with the lowest risk [25]. Similarly, a study of 9780 hospitalized patients by Thongprayoon et al. found that admission

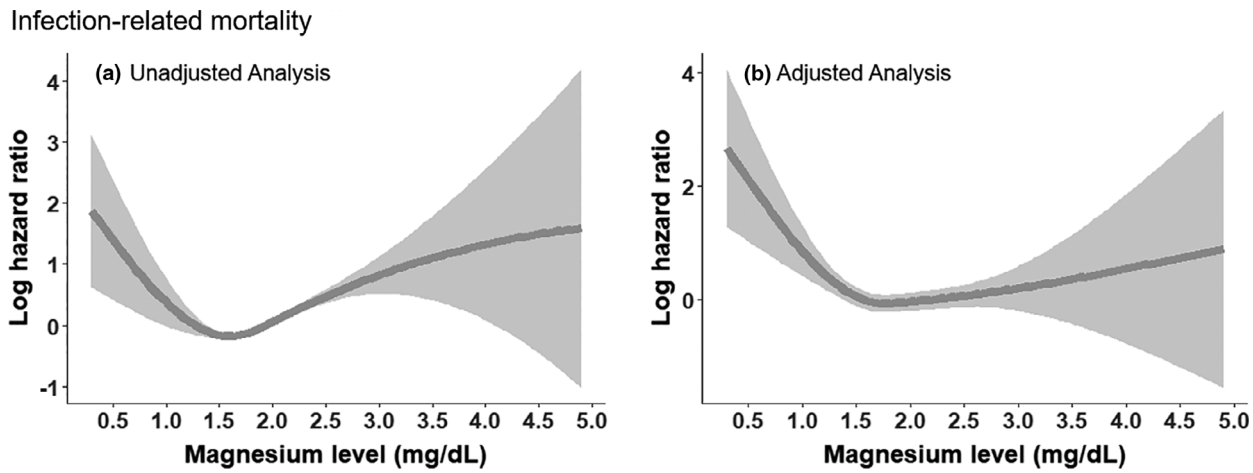

Figure 4 Relationship between serum Mg as a continuous variable and infection-related mortality for the unadjusted (a) and adjusted (b) analyses.

serum Mg between 1.7 and 1.9 mg/dl was associated with the lowest risk of developing acute respiratory failure [26].

It is also notable that the values associated with lowest risk are different than those in advanced CKD and ESKD patients. In a large study of over 10 000 patients with advanced CKD, serum Mg 1.7–2.6 mg/dl was associated with the lowest risk of death [27]. One limitation of their analysis is that Mg as a predictor variable was categorized as <1.7, 1.7–2.6, and >2.6 mg/dl, and not analyzed as a continuous variable. Another study including more than 140 000 ESKD patients on hemodialysis showed a similar U-curve for mortality, with the nadir at 2.7–2.9 mg/dl.[4] Compared to kidney transplant, ESKD is a completely different physiologic state with negligible to no renal Mg excretion, and the results may at least in part reflect the better nutritional status in patients with higher Mg levels. KTRs are often recommended low potassium diets, which inadvertently limits Mg intake. In addition, gastrointestinal losses due to diarrhea and PPIs, and urinary losses due to diuretics and CNIs are common, and may indeed be a marker of better dietary or medication compliance. Overall, these studies highlight that the optimal serum Mg range likely depends on the underlying disease state and that the curve may be shifted toward the right in those with poor kidney function and ESKD.

Our study has the limitations inherent to a retrospective, single-center study design. We may have residual confounding from kidney function as suggested by our sensitivity analyses and unmeasured variables such as peripheral vascular disease, cerebrovascular disease, and history of severe or opportunistic infections. Granular data on PPI and Mg supplement dose and duration were not available. In addition, serum Mg is an imperfect marker of total body Mg stores. Only 0.3% of total body Mg is intravascular. Small differences in serum Mg may reflect substantially larger differences in total body Mg stores. One major strength of our study was the use of time-dependent analysis which allowed us to better assess the association between serum Mg level over time and mortality, as risk was re-assessed every time a new serum Mg levels became available. In addition, our study is strengthened by large sample size, in terms of both patients (n = 3680) and serum Mg samples (n = 50 431).

In summary, in this study, we observed that serum Mg levels between 1.5 and 1.8 mg/dl are associated with lowest risk of mortality in KTRs. Further studies are needed to understand the higher risk associated with lower and higher Mg levels.

Authorship

Panthofer: concept, design, analysis, manuscript preparation, editing; Lyu: concept, design, analysis, manuscript preparation, editing; Astor: concept, design, analysis, manuscript preparation, editing; Singh: manuscript preparation, editing; Aziz: manuscript preparation, editing; Mandelbrot: manuscript preparation, editing; Parajuli: manuscript preparation, editing; Mohamed: manuscript preparation, editing; Djamali: manuscript preparation, editing; Garg: concept, design, analysis, manuscript preparation, editing.

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Conflict of interest

The authors have no conflict of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Serum Mg as a categorical variable.

Figure S1. Inclusion criteria.

Figure S2. Baseline serum Mg and all-cause mortality.

Figure S3. Baseline serum Mg and CVD-related mortality.

Figure S4. Baseline serum Mg and infection-related mortality.

Figure S5. Serum Mg as a time-dependent variable and all-cause mortality, stratified by baseline eGFR (<45 vs. ≥45 ml/min/1.73m^2).

Figure S6. Serum Mg as a continuous time-dependent variable and all-cause mortality; adjusted analysis including eGFR as a time-dependent covariate.

Figure S7. Median Mg during the baseline period and all-cause.

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