Association between hypomagnesemia and mortality among dialysis patients: a systematic review and meta-analysis

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Background. Malnutrition-inflammation-atherosclerosis (MIA) syndrome is caused by the inflammatory cytokines for end stage renal disease (ESRD) patients, and MIA complex-related factors may be associated to hypomagnesemia and mortality. However, the association between serum magnesium level and mortality for dialysis patients is still not clear. Additionally, no meta-analysis investigated the impact of serum magnesium on peritoneal dialysis and hemodialysis separately. Methods. We searched the published studies in PubMed, Embase, Cochrane, Collaboration Central Register of Controlled Clinical Trials, Cochrane Systematic Reviews until June, 2021. Studies associated with serum magnesium and all-cause mortality, cardiovascular (CV) mortality in ESRD on kidney replacement therapy (KRT) patients were included. Hazard ratio (HR) with 95% confidence intervals (CI) were used to report the outcomes. Results. Twenty-one studies involving 55232 patients were included. Overall, there was a significant association between hypomagnesemia and all-cause mortality for dialysis patients (HR: 1.672, 95% CI, [1.412-1.980], p<0.001; certainty of evidence: moderate), mixed unadjusted and adjusted HR for analysis. Besides, significantly increased risk of CV mortality for hypomagnesemia individuals compared with non-hypomagnesemia group (HR 1.574, 95% CI, [1.096-2.262, p<0.001; certainty of evidence: moderate). In addition, subgroup analysis demonstrated that hypomagnesemia was associated with a high risk of all-cause mortality and CV mortality (all-cause mortality, HR:1.80, 95% CI, [1.48-2.19]; CV mortality, HR:1.84, 95% CI, [1.10-3.07]) in the hemodialysis patients, but not in participants receiving peritoneal dialysis (all-cause mortality, HR:1.26, 95% CI, [0.84-1.91]; CV mortality, HR:0.66, 95% CI, [0.22-2.00]). Conclusions. Hypomagnesemia may be a significant risk factor for all-cause

mortality and CV mortality in KRT patients, especially those receiving hemodialysis. Because of the limited certainty of evidence, more studies are required to investigate its association.

Manuscript Title

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Abstract

Background. Malnutrition-inflammation-atherosclerosis (MIA) syndrome is caused by the inflammatory cytokines in end stage renal disease (ESRD) patients, and MIA complex-related factors may be associated with hypomagnesemia and mortality. However, the association between serum magnesium level and mortality for dialysis patients is still not clear. Additionally, no meta-analysis has investigated the impact of serum magnesium on peritoneal dialysis and hemodialysis, separately.

Methods. We searched published studies in PubMed, Embase, Cochrane, Collaboration Central Register of Controlled Clinical Trials, and Cochrane Systematic Reviews through April 2022. Studies associated with serum magnesium and all-cause mortality or cardiovascular (CV) mortality in ESRD on kidney replacement therapy (KRT) patients were included. A hazard ratio (HR) with 95% confidence intervals (CI) was used to report the outcomes.

Results. Twenty-one studies involving 55,232 patients were included. Overall, there was a

significant association between hypomagnesemia and all-cause mortality for dialysis patients (HR: 1.67, 95% CI, [1.412-2.00], p<0.001; certainty of evidence: moderate) using a mixed unadjusted and adjusted HR for analysis. There was also a significantly increased risk of CV mortality for individuals with hypomagnesemia compared with the non-hypomagnesemia group (HR 1.56, 95% CI, [1.08-2.25, p<0.001; certainty of evidence: moderate). In addition, a subgroup analysis demonstrated that hypomagnesemia was associated with a high risk of both all-cause mortality and CV mortality (all-cause mortality, HR:1.80, 95% CI, [1.48-2.19]; CV mortality, HR:1.84, 95% CI, [1.10-3.07]) in hemodialysis (HD) patients, but not in participants receiving peritoneal dialysis (PD; all-cause mortality, HR:1.26, 95% CI, [0.84-1.91]; CV mortality, HR:0.66, 95% CI, [0.22-2.00]). The systematic review protocol was prespecified and registered in PROSPERO [CRD42021256187].

Conclusions. Hypomagnesemia may be a significant risk factor for all-cause mortality and CV mortality in KRT patients, especially in those receiving hemodialysis. Because of the limited certainty of evidence, more studies are required to investigate this association.

Introduction

Hypermagnesemia is common in patients with end stage renal disease (ESRD) due to dialysate with a magnesium content of 0.5 mmol/L (Yang et al. 2021). Patients receiving regular dialysis may have hypomagnesemia because increased phosphate, sulfate, or other anions would decrease serum magnesium (Mg) levels by binding Mg and forming Mg complex. In Japan, about 0.38% of patients on hemodialysis have a serum Mg level less than 2.5 mg/dL (Sakaguchi et al. 2014). Among dialysis patients, magnesium deficiency has been associated with inflammation, hyperparathyroidism, insulin resistance-related diabetes mellitus, oxidative stress, atherosclerosis, and calcification of vascular smooth muscle cells (VSMC), which may lead to hypertension (Salem et al. 2012; Montes de Oca et al. 2014). A previous meta-analysis concluded that hypomagnesemia is significantly associated with all-cause and cardiovascular mortality in populations with chronic kidney disease (CKD) and ESRD without analyzing the outcomes for these two populations separately (Xiong et al. 2019).

Therefore, we defined hypomagnesemia as a serum Mg level less than 2.5mg/dL and conducted a meta-analysis to explore the associations among serum magnesium, all-cause mortality, and CV mortality in patients with ESRD on kidney replacement therapy (KRT).

Materials and Methods

Search strategy and selection criteria

71 This meta-analysis was conducted according to the Preferred Reporting Items of Systematic
72 Reviews and Meta-Analyses (PRISMA) statement (Higgins et al. 2011) and following the
73 Cochrane methods (Salguero et al. 2008). The protocol was prospectively submitted to
74 PROSPERO [CRD42021256187].
75 Two investigators (CY Huang; CC Yang) searched published studies in PubMed, Embase,
76 Cochrane, Collaboration Central Register of Controlled Clinical Trials, and Cochrane Systematic
77 Reviews until April 2022 without any language limitation (Data S1). Using Medical Subject
78 Headings (MeSH) terms and the PICO (population, intervention, comparison, outcome), we
79 selected key words such as “Renal Dialysis,” “Hemodialysis,” “Peritoneal dialysis,”
80 “Magnesium,” “Hypomagnesemia,” “Hypermagnesemia,” “Mortality,” and “Death” as search
81 terms for our literature review. Prospective and retrospective cohort studies and observational
82 studies were included, but case reports and case series were excluded. Two investigators (CY
83 Huang, CC Yang) independently performed searches and checked all articles for inclusion. If
84 they disagreed on the inclusion of an article, a third author (MY, Jiang) resolved the dispute.
85 **Inclusion and exclusion criteria**
86 Published studies were included if they: (1) reported the impact of serum magnesium on all-
87 cause or CV mortality for KRT patients; (2) used a cohort study design, including retrospective
88 (e.g., cohort and case control study) and prospective cohort studies; and (3) reported the hazard

ratio (HR) with 95% confidence intervals (CIs) or provided sufficient data to investigate the outcomes. The following studies were excluded: (1) studies that did not include the outcomes of CV mortality or all-cause mortality, or (2) had follow-up times less than 12 months.

Data extraction

The following data were extracted from the articles: first author, year of publication, patient characteristics (sample size, age, and sex), follow-up duration, and clinical outcomes. Both abstracts and full papers were selected for quality assessment and data synthesis. If the data were incomplete in the text but extractable from the figures (ex. Kaplan-Meier (KM) survival curve), we used WebPlotDigitizer Version 4.1 to extrapolate the data (Drevon et al. 2017). Another author (YT, Huang) then verified these data. We did our best to contact the corresponding authors for more information about the selected studies.

Quality assessment

The risk of bias of the included studies was assessed by two authors (CC, Hsieh; MH, Chuang), independently, using the Newcastle-Ottawa Scale (NOS). The NOS contains three domains which consisted of eight items totally, which represent three quality assessment parameters: selection, comparability, and outcome. One point was given for a low risk of bias, and 0 points were given for a high or unclear risk of bias. A score of 0–3 points was considered to be a low-quality study, a score of 4–6 points equated to a moderate-quality study, with a score of 7–9

points indicating a study was high quality.

Outcomes and definition of hypomagnesemia or non-hypomagnesemia

The primary outcome of this meta-analysis was all-cause mortality, with CV mortality as a secondary outcome. Individual trials had different serum magnesium cut-off values for defining hypomagnesemia and non-hypomagnesemia in KRT patients. Among these studies, the HRs of serum magnesium as dichotomous variables were regarded as "lower magnesium vs. non-hypomagnesium," according to their respective categories.

Data synthesis and statistical analysis

The random-effects model was employed to analyze the selected outcomes (all-cause mortality and CV mortality) between the two groups. The effect size was expressed as the pool HRs with 95% CIs.

We used funnel plots to demonstrate potential publication bias. Statistical heterogeneity was calculated using I^2, with an I^2 more than 50% indicating the studies were not homogeneous. P-values < 0.05 were considered statistically significant. We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of the evidence for each outcome. We used the Comprehensive Meta-Analysis software (Version 3.3.070, November 20, 2014) for all statistical analyses.

Subgroup analysis

We performed subgroup analyses of adjusted/unadjusted outcomes, dialysis modality (HD, PD), serum magnesium cut-off value for defining the hypomagnesemia and non-hypomagnesemia groups (1.58-2.5 mg/dL vs. 2.5-2.79 mg/dL), follow-up period (>= 5 years vs. < 5 years), study design (retrospective vs. prospective), and if the data were extracted from the KM survival curve.

Results

Search results and included studies

Our initial screening of cohort studies focused on published studies that were available on May 20th, 2021. We then submitted our study to PROSPERO and completed our comprehensive database collection on April 4th, 2022.

A total of 3,416 studies were identified from the databases and 224 studies were identified from registers as original research. We removed 810 studies due to duplication. Of the remaining 2,830 articles, a further 2,806 articles were excluded after reviewing the title and abstract (Figure 1). The remaining 24 studies were then assessed for eligibility. After excluding three more studies that lacked usable data for an analysis, a total of 21 observational studies of 55,232 patients undergoing dialysis were selected for inclusion in the final meta-analysis.

Study characteristics

As shown in table 1, the included studies were published from 2007 to 2020, including twelve studies from Asia (Ishimura et al. 2007; Kurita et al. 2015; Ago et al. 2016; Cai et al. 2016; Yang

et al. 2016; Ye et al. 2018; Mizuiri et al. 2019; Shimohata et al. 2019; Tamura et al. 2019; Wu et al. 2019; Lu et al. 2020; Mizuiri et al. 2020), seven from Europe (Markaki et al. 2012); (Vervloet 2013) (João Matias et al. 2014); (Lacson et al. 2015); (de Roij van Zuijdewijn et al. 2015); (Garagarza et al. 2015); (Selim et al. 2017), and two from North America (Fein et al. 2014; Li et al. 2015). Thirteen studies were retrospective studies (Ishimura et al. 2007; Fein et al. 2014; de Roij van Zuijdewijn et al. 2015; Lacson et al. 2015; Ago et al. 2016; Cai et al. 2016; Li et al. 2016; Yang et al. 2016; Mizuiri et al. 2019; Shimohata et al. 2019; Wu et al. 2019; Lu et al. 2020; Mizuiri et al. 2020), and the other eight studies were prospective studies (Markaki et al. 2012; Vervloet 2013; João Matias et al. 2014; Garagarza et al. 2015; Kurita et al. 2015; Selim et al. 2017; Ye et al. 2018; Tamura et al. 2019)

Hemodialysis (HD) patients were the study population in fifteen studies, (Ishimura et al. 2007; João Matias et al. 2014; de Roij van Zuijdewijn et al. 2015; Garagarza et al. 2015; Kurita et al. 2015; Lacson et al. 2015; Li et al. 2015; Ago et al. 2016; Selim et al. 2017; Mizuiri et al. 2019; Shimohata et al. 2019; Tamura et al. 2019; Wu et al. 2019; Lu et al. 2020; Mizuiri et al. 2020), peritoneal dialysis (PD) patients were the study population in four studies (Fein et al. 2014; Cai et al. 2016; Yang et al. 2016; Ye et al. 2018), and two studies had a study population that combined HD and PD patients (Markaki et al. 2012; Vervloet 2013). The mean ages of the HD and PD populations were 62±6 and 55±6 years, respectively. The follow-up duration of the 21

included studies ranged from 12 to 129.6 months, with one study not reporting the follow-up duration (Garagarza et al. 2015). Twenty studies reported the association of serum magnesium and all-cause mortality (Ishimura et al. 2007; Markaki et al. 2012; Fein et al. 2014; João Matias et al. 2014; de Roij van Zuijdewijn et al. 2015; Garagarza et al. 2015; Kurita et al. 2015; Lacson et al. 2015; Li et al. 2015; Ago et al. 2016; Cai et al. 2016; Yang et al. 2016; Selim et al. 2017; Ye et al. 2018; Mizuiri et al. 2019; Shimohata et al. 2019; Tamura et al. 2019; Wu et al. 2019; Lu et al. 2020; Mizuiri et al. 2020) and nine studies reported the association of serum magnesium and CV mortality (Ishimura et al. 2007; Vervloet 2013; João Matias et al. 2014; de Roij van Zuijdewijn et al. 2015; Cai et al. 2016; Ye et al. 2018; Mizuiri et al. 2019; Tamura et al. 2019; Lu et al. 2020). The cut-off value of serum magnesium used for defining hypomagnesemia ranged from 1.7 to 2.77 mg/dl.

Heterogeneity and publication bias

The heterogeneity was 82.77% for all-cause mortality and 71.46% for CV mortality according to the I^2 test. Publication bias, as evaluated using funnel plots and Egger's test, was significant for all-cause mortality (Figure S1), but not significant for CV mortality (Figure S2). We used subgroup analyses and meta-regression to investigate the observed heterogeneity.

Quality of enrolled trials

The NOS score of the included studies was 6-9 (Table S1), with 20 of the 21 studies reaching the

high-quality NOS score range of 7-9. The one study that did not reach a score between 7-9 (Garagarza et al. 2015) received a score of six points. This study was considered to be of moderate quality because it did not include the follow-up duration of the study. There was a high inter-observer reliability in article selection (Kappa coefficient=0.90).

Assessment of evidence quality and summary of findings

An evidence quality assessment was performed using the GRADE system for the outcomes of all-cause mortality and CV mortality (Table S3).

Serum magnesium and all-cause mortality

Twenty studies of 54,471 KRT patients reported the association between serum magnesium levels and all-cause mortality. Ten studies presented both unadjusted and adjusted HR (de Roij van Zuijdewijn et al. 2015; Kurita et al. 2015; Li et al. 2015; Ago et al. 2016; Cai et al. 2016; Yang et al. 2016; Selim et al. 2017; Shimohata et al. 2019; Wu et al. 2019; Mizuiri et al. 2020), seven studies included only adjusted HR (Ishimura et al. 2007; Markaki et al. 2012; Fein et al. 2014; João Matias et al. 2014; Garagarza et al. 2015; Ye et al. 2018; Lu et al. 2020), and three studies included only unadjusted HR (Lacson et al. 2015; Mizuiri et al. 2019; Tamura et al. 2019). Four studies extracted data for the HR calculation from the KM survival curve (Table 2; (Fein et al. 2014; Mizuiri et al. 2019; Tamura et al. 2019; Lu et al. 2020; Mizuiri et al. 2020).

The results of our meta-analysis showed that hypomagnesemia was associated with increased

risk of all-cause mortality compared with non-hypomagnesemia among KRT patients [random effect, HR:1.67, 95% CI: [1.41-2.00], p<0.001, (Figure 2A)]. However, we found high heterogeneity among the included studies (random effect model, I^2 value of 82.77**%**, Figure 2A).

Serum magnesium and cardiovascular mortality

Nine out of the 21 studies reported the relationship between serum magnesium level and CV mortality among dialysis patients (Ishimura et al. 2007; Vervloet 2013; João Matias et al. 2014; de Roij van Zuijdewijn et al. 2015; Cai et al. 2016; Ye et al. 2018; Mizuiri et al. 2019; Tamura et al. 2019; Lu et al. 2020). Four of these studies presented both unadjusted and adjusted HR (João Matias et al. 2014; de Roij van Zuijdewijn et al. 2015; Cai et al. 2016; Ye et al. 2018), three included only unadjusted HR (Tamura et al. 2019; Lu et al. 2020; Mizuiri et al. 2020), and the remaining two studies only included adjusted HR (Ishimura et al. 2007; Vervloet 2013). One of these studies extracted data for the HR calculation from the KM survival curve. The results of this meta-analysis showed an increased risk of CV mortality for dialysis patients with hypomagnesemia compared to those with non-hypomagnesemia. [random effect, HR:1.56, 95% CI: [1.08-2.25], p<0.001, (Figure 2B)]. However, we found high heterogeneity among the included studies (random effect model, I^2 value of 71.46%, Figure 2B).

Subgroup analysis

A subgroup analysis showed that the association between hypomagnesemia and increased all-

cause mortality (Figure 3A) and CV mortality (Figure 3B) among dialysis patients was consistently significant when stratified by follow-up duration and data extraction. A subgroup analysis by dialysis modality revealed that hypomagnesemia was associated with increased all-cause and CV mortality among HD patients, but this association was not present among PD patients. In addition, while the associations between hypomagnesemia and all-cause mortality were significant for serum magnesium cut-off values both above and below 2.5mg/dL, the association between hypomagnesemia and CV mortality was only significant for a cut-off value less than 2.5mg/dL.

Meta-regression analysis

The quantitative measures of serum magnesium levels, older age, prevalence of diabetes, or male proportion were not associated with all-cause mortality (Age, Z = 0.12, P = 0.90, Figure S3A; DM, Z=-1.27; P=0.205, Figure S3B; Male, Z=0.35, P=0.72, Figure S3C; the quantitative measures of serum levels of Mg, Z=0.95, P=0.34) or CV mortality (Age, Z = 0.29, P = 0.7685, Figure S4A; DM, Z=0.75; P=0.4548, Figure S4B; Male, Z=1.69, P=0.0.0907, Figure S4C; the quantitative measures of serum levels of Mg, Z=0.91, P=0.3636) between the hypomagnesemia and non-hypomagnesemia groups (Table S4).

Discussion

In this meta-analysis of twenty-one studies, our results showed that hypomagnesemia is associated with an increased risk of all-cause mortality and CV mortality among KRT patients. When stratified by dialysis modality, hypomagnesemia was associated with increased all-cause and CV mortality among HD patients, but this association was not significant among PD patients. Additionally, if the cut-off value of serum magnesium was higher than 2.5 mg/dl, hypomagnesemia did not significantly correlate with an increased risk of CV mortality among dialysis patients. Several mechanisms could explain the increased risk of all-cause mortality/CV mortality with serum magnesium deficiency. First, hypomagnesemia is associated with, and may lead to metabolic syndrome and insulin resistance (Volpe 2008). Because magnesium is involved in over 300 enzymatic reactions, magnesium deficiency can contribute to the defective tyrosine kinase activities of insulin receptors (Suárez et al. 1995), impairment of modulating insulin-mediated glucose uptake and vascular tone (Barbagallo et al. 2003), elevation of tumor necrosis factor-alpha (Rodriguez-Morán & Guerrero-Romero 2004), and CRP levels (Dibaba et al. 2014). Additionally, ESRD patients in the presence of hypomagnesemia have elevated levels of adiponectin, which plays a role in energy homeostasis and lipid/glucose metabolism (Markaki et al. 2012) and may correlate with ischemic heart disease (van de Wal-Visscher et al. 2018). Hypomagnesemia is also related to defect immunity, involving both innate and acquired immune responses (Tam et al. 2003). The molecular identification of multiple magnesium transporters

has provided the basis for the role magnesium plays in the immune system (Brandao et al. 2013). A low magnesium level inhibits endothelial proliferation by generating an inflammatory, pro-thrombotic, pro-atherogenic environment, which could be a contributor to the pathogenesis of cardiovascular disease (Maier et al. 2004). Patients with hypomagnesemia may have a higher risk of electrolyte imbalances such as hypokalemia or hypocalcemia, because dialysis patients with imbalances and an inadequate protein and energy intake develop protein-energy wasting (PEW; (Maraj et al. 2018). Acute nutritional depletion seems to be related to poor appetite with low food intake and may be the cause of hypokalemia and hypocalcemia in dialysis patients (Vavruk et al. 2012). These electrolyte imbalances can cause cardiac arrhythmias (Hansen & Bruserud 2018). A diet high in green leafy vegetables, cereals, and nuts abundant in magnesium might help prevent hypomagnesemia-related mortality in dialysis patients (Chrysant & Chrysant 2019). Closely tracking serum magnesium levels is also an important strategy for preventing hypomagnesemia in dialysis patients.

In this meta-analysis, hypomagnesemia had a significant association with all-cause mortality/CV mortality for HD patients, but no obvious association was observed in PD patients in a subgroup analysis (Markaki et al. 2012; Fein et al. 2014; Cai et al. 2016; Yang et al. 2016). This could be because hemodynamic fluctuation happens in the intermittent delivery of HD due to the rapid loss of residual renal function and HD-induced myocardial and cerebral ischemia (Selby &

Kazmi 2019).

Another subgroup analysis revealed that while the associations between hypomagnesemia and all-cause mortality were significant for serum magnesium cut-off values both above and below 2.5mg/dL, the association between hypomagnesemia and CV mortality was only significant for a cut-off value less than 2.5mg/dL. (Courivaud & Davenport 2014) reported that mild hypermagnesemia may have a protective effect in reducing soft tissue and vascular calcification, while higher serum magnesium may be the consequence of better nutrition status (Joffres et al. 1987). These findings may help explain why a lower serum magnesium cut-off value (<= 2.5 mg/dl) was associated with a higher risk of CV mortality when a lower cut-off value (> 2.5 mg/dl) was not (Courivaud & Davenport 2014).

According to the 2020 United States Renal Data System Annual Data Report: Epidemiology of Kidney Disease, individuals with end stage renal disease (ESRD) undergoing dialysis have a higher risk of cardiovascular disease and a shorter life expectancy than the general population. The traditional risk factors of cardiovascular disease among dialysis patients include diabetes, hypertension, and smoking, while malnutrition, chronic inflammation, and vascular calcification are considered non-traditional risk factors (Menon et al. 2005); (Choi et al. 2019); (Cozzolino et al. 2018); (Allawi 2018). Among dialysis patients, magnesium deficiency has been shown to correlate with atherosclerosis and calcification of VSMC (Salem et al. 2012; Montes de Oca et

al. 2014). A previous meta-analysis concluded that hypomagnesemia is significantly associated with all-cause and cardiovascular mortality in patients with chronic kidney disease (CKD) and ESRD, though the analysis did not analyze the outcomes for these two populations separately (Xiong et al. 2019). Another meta-analysis demonstrated that hypomagnesemia was closely related to an increase in all-cause mortality in hemodialysis (HD) patients, but the impact of serum magnesium on peritoneal dialysis (PD) patients was not discussed. This meta-analysis also did not investigate the diverse cut-off values of serum magnesium among the included studies (Liu & Wang 2021). Because of these existing gaps in the published research, we conducted a meta-analysis about the association of serum magnesium with all-cause mortality and CV mortality in patients with ESRD on KRT. **Strengths and Limitations**

Our study has some significant strengths. This is the first meta-analysis comprehensively evaluating the association of serum magnesium concentration on all-cause mortality and CV mortality in dialysis patients, specifically. Our findings represent the current evidence supporting the potential influence of hypomagnesemia on relevant clinical outcomes. We also extracted data from the KM survival curve using the WebPlotDigitizer, making our data more complete.

However, our study results should be interpreted cautiously because of its limitations. First, a high heterogeneity was observed among the included studies, which could be related to differences among the studies in serum magnesium cut-off values and follow-up period lengths.

Two included studies (Vervloet 2013; Garagarza et al. 2015) were only available as abstracts and were thus lacking complete, available data. The inclusion criteria for patients also differed among the included studies. For example, the proportion of diabetes was vastly different among the studies, with one study even excluding DM patients (Shimohata et al. 2019). These inclusion differences mean the patients included in this meta-analysis may not match the characteristics of real-world patients on dialysis. Two of the included studies (Markaki et al. 2012; Vervloet 2013) combined the data for both HD and PD patients, which may interfere with the analyses of HD and PD patients, separately. More studies investigating the relationship between serum magnesium and clinical outcomes in PD patients, specifically, are needed. In three of the included studies (Kurita et al. 2015; Lacson et al. 2015);(Yang et al. 2016), participants were separated into multiple serum magnesium subgroups (ex. low, middle, higher groups). For these studies, we compared the outcomes of the lowest and the highest magnesium groups, which may have induced relevant bias in the effect estimates.

Conclusions

In our meta-regression analysis, the quantitative measures of serum magnesium levels, age, sex, or prevalence of diabetes were not associated with all-cause mortality or CV mortality. Our study suggested that a lower magnesium concentration is associated with a significant risk of all-cause mortality and CV mortality compared with non-hypomagnesemia serum magnesium levels in

dialysis participants. Hypomagnesemia had a larger impact on the clinical outcomes of HD patients than for PD patients, but additional studies investigating serum magnesium levels in PD patients are required.

Acknowledgements

Thank for all the staff of division Nephrology, Internal medicine department of Chi Mei Medical Center, with valuable opinion for this study.

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Legend:

Figure 1:

Flowchart of study selection for meta-analysis.

Figure 2:

Forest plot showing increased risk of (A) all-cause mortality (B) cardiovascular mortality, comparing hypoMg versus non-hypoMg in a population of dialysis patients. Random effects of Mantel-Haenszel model.

Abbreviations: CI, confidence intervals; hypoMg, hypomagnesemia

Figure 3:

Subgroup analysis for (A) all-cause mortality, (B) cardiovascular mortality comparing hypoMg versus non-hypoMg in a population of dialysis patients.

Abbreviations: CI, confidence intervals; hypoMg, hypomagnesemia

513 Table 1:

514 Summary of the baseline characteristics of the included studies

515

516 Table 2:

517 Summary of the outcome of the included studies

Figure 1

Flowchart of study selection for meta-analysis.

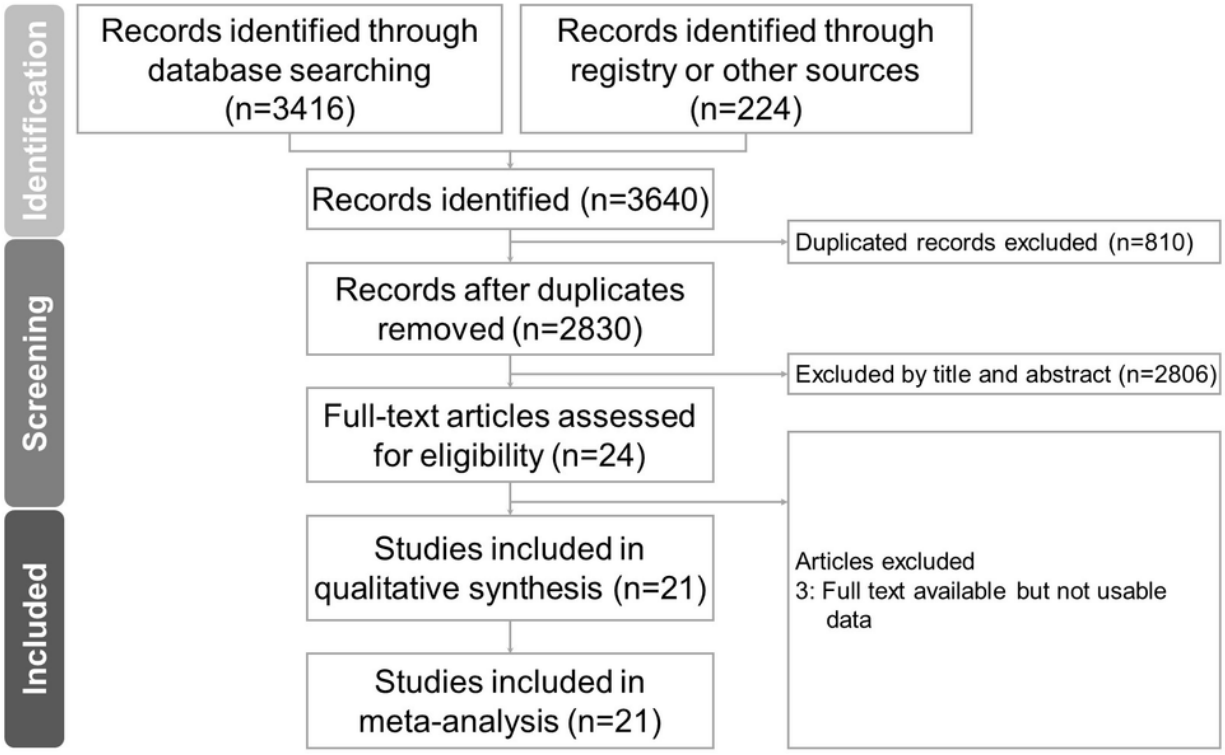


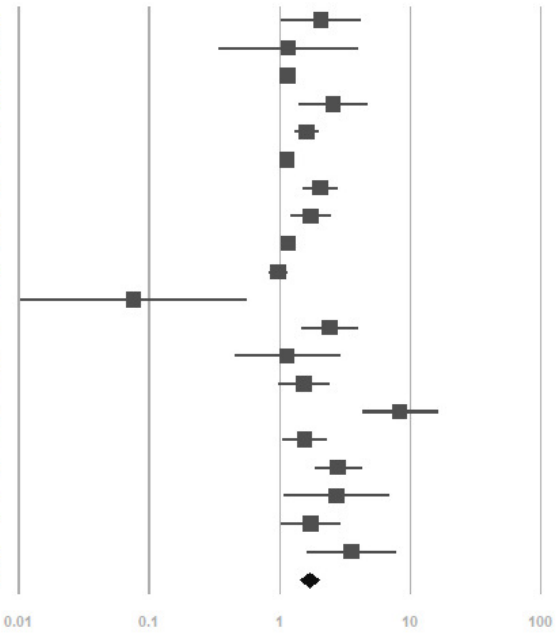
Figure 2

Forest plot showing increased risk of (A)all-cause mortality (B)cardiovascular mortality, comparing hypoMg versus non-hypoMg in a population dialysis patients.

A.

Random effect model

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Ishimura (2007)	2.060	1.026	4.135	2.033	0.042	3.49
Markaki(2012)	1.160	0.340	3.959	0.237	0.813	1.56
Matias(2014)	1.149	1.005	1.314	2.034	0.042	8.09
Fein(2014)	2.550	1.398	4.652	3.051	0.002	4.11
Lacson(2015)	1.600	1.303	1.965	4.487	0.000	7.57
de Roij van Zuijdewijn(2015)	1.140	1.013	1.283	2.168	0.030	8.17
Garagarza(2015)	2.040	1.508	2.759	4.629	0.000	6.70
Kurita(2015)	1.730	1.201	2.492	2.943	0.003	6.10
Li(2016)	1.170	1.051	1.302	2.882	0.004	8.24
Yang(2016)	0.970	0.814	1.156	-0.341	0.733	7.80
Cai(2016)	0.075	0.010	0.557	-2.531	0.011	0.66
Ago(2016)	2.410	1.461	3.975	3.445	0.001	4.88
Selim(2017)	1.140	0.445	2.922	0.273	0.785	2.35
Ye(2018)	1.530	0.980	2.389	1.870	0.061	5.36
Wu(2019)	8.300	4.258	16.181	6.213	0.000	3.66
Tamura(2019)	1.550	1.040	2.310	2.153	0.031	5.78
Mizuiri(2019)	2.790	1.831	4.250	4.778	0.000	5.58
Shimohata(2019)	2.730	1.072	6.953	2.106	0.035	2.37
Mizuiri(2020)	1.720	1.007	2.939	1.984	0.047	4.60
Lu(2020)	3.535	1.592	7.849	3.103	0.002	2.95
Total	1.670	1.410	1.979	5.939	0.000	

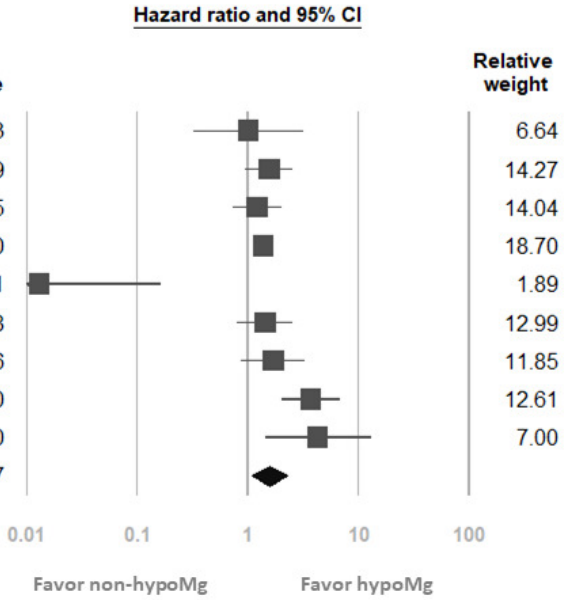


Heterogeneity: df(Q):19, P value: <0.001, I^2=82.772%
Tau-squared:0.088, Standard error:0.056, Variance:0.003

B.

Random effect model

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Ishimura (2007)	1.020	0.323	3.220	0.034	0.973	6.64
Broek(2013)	1.560	0.950	2.561	1.758	0.079	14.27
Matias(2014)	1.220	0.732	2.033	0.763	0.445	14.04
de Roij van Zuijdewijn(2015)	1.370	1.173	1.600	3.972	0.000	18.70
Cai(2016)	0.013	0.001	0.162	-3.375	0.001	1.89
Ye(2018)	1.430	0.799	2.558	1.205	0.228	12.99
Tamura(2019)	1.698	0.877	3.289	1.570	0.116	11.85
Mizuiri(2019)	3.730	2.031	6.849	4.245	0.000	12.61
Lu(2020)	4.285	1.421	12.920	2.584	0.010	7.00
Total	1.563	1.084	2.252	2.394	0.017	

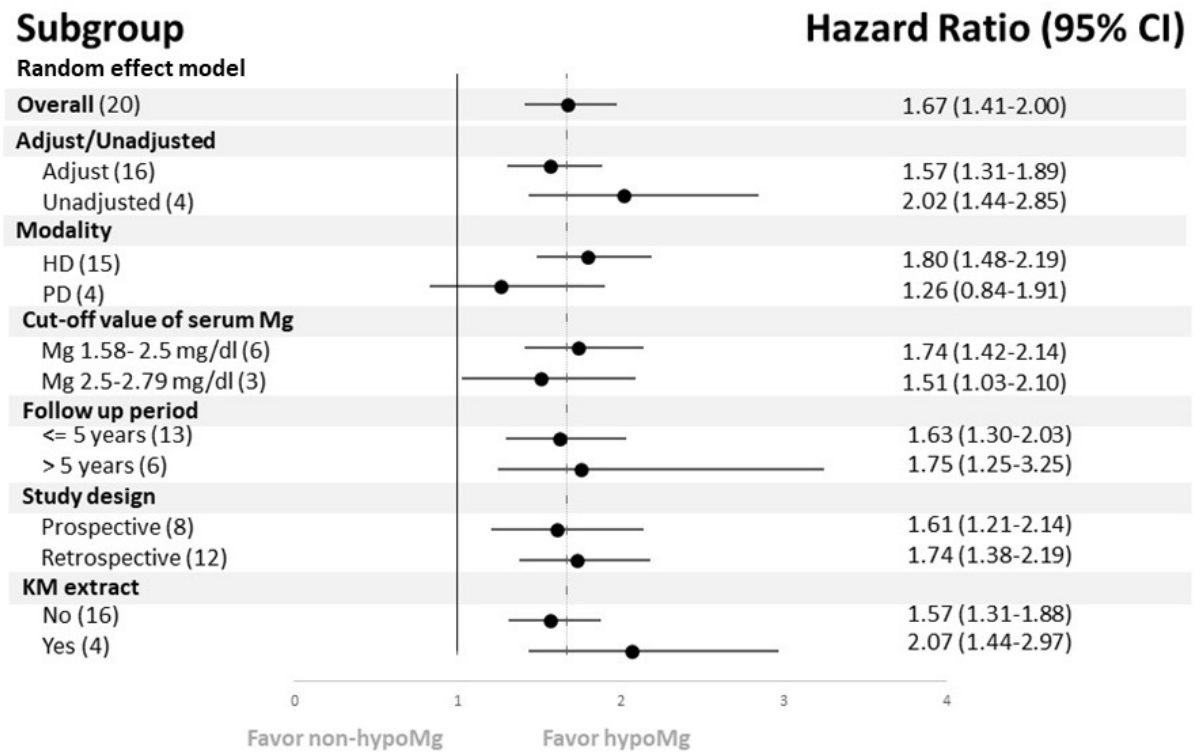


Heterogeneity: df(Q):8, P value: <0.001, I^2=71.46%
Tau-squared:0.180, Standard error:0.165, Variance:0.027

Figure 3

Figure 3. Subgroup analysis for (A)all-cause mortality (B)cardiovascular mortality comparing hypoMg versus non-hypoMg in a population of dialysis patients.

A.


Subgroup
Hazard Ratio (95% CI)
Random effect model
Overall (20)
1.67 (1.41-2.00)
Adjust/Unadjusted
Adjust (16)
1.57 (1.31-1.89)
Unadjusted (4)
2.02 (1.44-2.85)
Modality
HD (15)
1.80 (1.48-2.19)
PD (4)
1.26 (0.84-1.91)
Cut-off value of serum Mg
Mg 1.58- 2.5 mg/dl (6)
1.74 (1.42-2.14)
Mg 2.5-2.79 mg/dl (3)
1.51 (1.03-2.10)
Follow up period
<= 5 years (13)
1.63 (1.30-2.03)
> 5 years (6)
1.75 (1.25-3.25)
Study design
Prospective (8)
1.61 (1.21-2.14)
Retrospective (12)
1.74 (1.38-2.19)
KM extract
No (16)
1.57 (1.31-1.88)
Yes (4)
2.07 (1.44-2.97)
0
1
2
3
4
Favor non-hypoMg
Favor hypoMg

B.

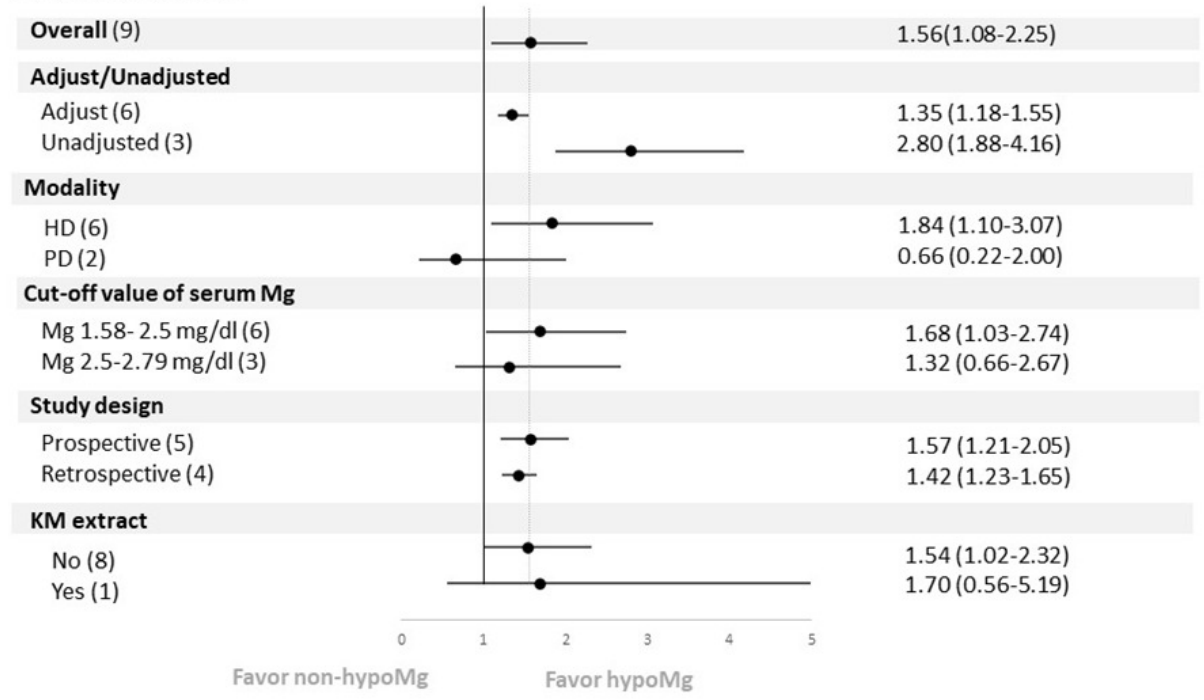

Random effect model
Overall (9)
1.56(1.08-2.25)
Adjust/Unadjusted
Adjust (6)
1.35 (1.18-1.55)
Unadjusted (3)
2.80 (1.88-4.16)
Modality
HD (6)
1.84 (1.10-3.07)
PD (2)
0.66 (0.22-2.00)
Cut-off value of serum Mg
Mg 1.58- 2.5 mg/dl (6)
1.68 (1.03-2.74)
Mg 2.5-2.79 mg/dl (3)
1.32 (0.66-2.67)
Study design
Prospective (5)
1.57 (1.21-2.05)
Retrospective (4)
1.42 (1.23-1.65)
KM extract
No (8)
1.54 (1.02-2.32)
Yes (1)
1.70 (0.56-5.19)
0
1
2
3
4
5
Favor non-hypoMg
Favor hypoMg

Table 1(on next page)

Summary of the baseline characteristics of the included studies

Table 1. Summary of the baseline characteristics of the included studies

Author	Nation	Study Design	Modality	Population(n)	Male(%)	DM(%)	*Age (years)	Follow up duration (m)	cut-off value of serum Mg (mg/dL)
Ishimura[15](2007)	Japan	Retrospective	HD	515	59.4	24.0	60±12	51	2.77
Markaki[24](2012)	Greece	Prospective	HD+PD	74	55.4	18.9	65±15	50	2.45
Vervloet[25](2013)	Germany	Prospective	HD+PD	761	59.0	25.0	63±14	36	2.07
Matias[26](2014)	Portugal	Prospective	HD	206	55.0	26.0	63.6±14.3	48	2.79
Fein[32](2014)	United States	Retrospective	PD	62	45.0	25.0	55±16	129.6	1.94
Lacson[27](2015)	Germany	Retrospective	HD	27544	53.7	53.6	61.9±15	12	1.58
de Roij van Zuijdewijn[28](2015)	Netherlands	Retrospective	HD	365	61.9	20.8	64.1±13.7	36	2.07
Garagarza[29](2015)	Portugal	Prospective	HD	605	NR	NR	69.9	NR	2.0
Kurita[16](2015)	Japan	Prospective	HD	2185	62.0	26.0	61.7±12.5	36	2.3
Li[33](2015)	United States	Retrospective	HD	9359	56.2	59.1	63.3±14.9	60	2.0
Yang[17](2016)	China	Retrospective	PD	10692	55.0	63.0	56±16	13	1.8
Cai[18](2016)	China	Retrospective	PD	253	55.3	22.9	58±16	29	1.7
Ago[19](2016)	Japan	Retrospective	HD	399	63.2	35.3	65.86±11.8	12	2.2
Selim[30](2017)	Republic of Macedonia	Prospective	HD	185	59.5	17.3	49.7±14.7	60	2.67
Ye[20](2018)	China	Prospective	PD	402	57.0	20.6	49.3±14.9	49.9	1.7
Wu[21](2019)	China	Retrospective	HD	169	53.8	NR	60.20 ± 15.64	120	2.43
Tamura[12](2019)	Japan	Prospective	HD	392	65.3	47.2	68	43.5	2.6
Mizuiri_2[13](2019)	Japan	Retrospective	HD	353	66.6	40.2	68	36	2.4
Shimohata[22](2019)	Japan	Retrospective	HD	83	62.1	0	58	120	2.5
Mizuiri[14](2020)	Japan	Retrospective	HD	215	67.9	44.2	73	36	2.3

Lu[23](2020)	China	Retrospective	HD	413	57.4	14.4	50.4±14.3	12	2.43

*Data of age are presented as mean ± standard deviation

Abbreviations: DM, Diabetes Mellitus; HD, Hemodialysis; m, month; Mg, Magnesium; mg/dl, milligrams per deciliter; NR, not reported; PD, Peritoneal dialysis

Table 2(on next page)

Summary of the outcome of the included studies

Table 2 Summary of the outcome of the included studies

Author	all-cause mortality, HR (95%CI)	CV mortality, HR (95%CI)	Primary outcome	Secondary outcome	Study quality, NOS
Ishimura[15] (2007)	2.060[a] (1.026-4.135)	1.020[a] (0.323-3.220)	all-cause mortality	CV mortality	9
Markaki[24] (2012)	1.160[a] (0.340-3.959)	NR	all-cause mortality	NR	7
Vervloet Broek[25] (2013)	NR	1.560[a] (0.950-2.561)	all-cause and CV mortality	NR	7
Matias[26] (2014)	1.149[a] (1.005-1.314)	1.220[a] (0.732-2.033)	all-cause and CV mortality	NR	8
Fein[32] (2014)	2.550[b] (1.398-4.652)	NR	all-cause mortality	NR	9
Lacson[27] (2015)	1.600 (1.303-1.965)	NR	all-cause mortality	NR	8
de Roij van Zuijdewijn[28] (2015)	1.140 (1.013-1.283)	1.370[a] (1.173-1.600)	all-cause and CV mortality	NR	9
Garagarza[29] (2015)	2.040[a] (1.508-2.759)	NR	all-cause mortality	NR	6
Kurita[16] (2015)	1.730 (1.201-2.492)	NR	all-cause mortality	NR	7
Li[33] (20165)	1.170[a] (1.051-1.302)	NR	all-cause mortality	NR	9
Yang[17] (2016)	0.970[a] (0.814-1.156)	NR	all-cause mortality	NR	9
Cai[18] (2016)	0.075[a] (0.010-0.557)	0.013[a] (0.001-0.162)	all-cause and CV mortality	NR	9
Ago[19] (2016)	2.410[a] (1.461-3.975)	NR	all-cause mortality	NR	7
Selim[30] (2017)	1.140[a] (0.445-2.922)	NR	all-cause and CV mortality	NR	8
Ye[20] (2018)	1.530[a] (0.980-2.389)	1.430[a] (0.799-2.558)	CV mortality	All-cause mortality	8
Wu[21] (2019)	8.300[a] (4.258-16.181)	NR	all-cause and CV mortality	NR	9
Tamura[12] (2019)	1.550[b] (1.040-2.310)	1.698[b] (0.877-3.289)	all-cause mortality	CV mortality	8
Mizuiri_2[13] (2019)	2.790 (1.831-4.250)	3.730 (2.031-6.849)	all-cause mortality	NR	8
Shimohata[22] (2019)	2.730[a] (1.072-6.953)	NR	all-cause mortality	NR	7
Mizuiri[14] (2020)	1.720[b] (1.007-2.939)	NR	all-cause mortality	NR	8
Lu[23] (2020)	3.535190[b] (1.594606-7.8386.335)	3.690[b]4.285 –(1.42532-	all-cause and CV mortality	NR	7

		12.9108.890)			

a. adjust HR; b. data extracted from Kaplan-Meier survival curve

Abbreviations: CV, cardiovascular; HR, hazard ratio; NOS, Newcastle-Ottawa Scale; NR, Not reported;