

Prognostic Value of Serum Magnesium in Mortality Risk among Patients on Hemodialysis: A Meta-Analysis of Observational Studies

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Keywords

Serum magnesium · Mortality · Hemodialysis · Meta-analysis

Abstract

Background: Previous studies have reported that serum magnesium (Mg) deficiency is involved in the development of heart failure, particularly in patients with end-stage kidney disease. The association between serum Mg levels and mortality risk in patients receiving hemodialysis is controversial. We aimed to estimate the prognostic value of serum Mg concentration on all-cause mortality and cardiovascular mortality in patients receiving hemodialysis. **Methods:** We did a systematic literature search in PubMed, EMBASE, Cochrane Library, and Web of Science to identify eligible studies that reported the prognostic value of serum Mg levels in mortality risk among patients on hemodialysis. We performed a meta-analysis by pooling and analyzing hazard ratios (HRs) and 95% confidence intervals (CIs). **Results:** We identified 13 observational studies with an overall sample of 42,967 hemodialysis patients. Higher all-cause mortality (adjusted HR 1.58

[95% CI: 1.31–1.91]) and higher cardiovascular mortality (adjusted HR 3.08 [95% CI: 1.27–7.50]) were found in patients with lower serum Mg levels after multivariable adjustment. There was marked heterogeneity ($I^2 = 79.6\%$, $p < 0.001$) that was partly explained by differences in age stratification and study area. In addition, subgroup analysis showed that a serum Mg concentration of ≤ 1.1 mmol/L might be the vigilant cutoff value. **Conclusion:** A lower serum Mg level was associated with higher all-cause mortality and cardiovascular mortality in patients receiving hemodialysis.

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Introduction

Magnesium ion (Mg^{2+}) is important for maintaining neuromuscular irritability and participates in multiple physiological activities, including material and energy metabolism [1]. Previous studies indicated that Mg^{2+} de-

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iciency was associated with an increased incidence of diabetes mellitus, metabolic syndrome, myocardial infarction, and stroke [2–5] by mediating vascular constriction, platelet aggregation, inflammation, and oxidative stress [6, 7], showing that Mg^{2+} is indispensable in homeostasis.

Magnesium plays a significant role in the function of the cardiovascular system [8]. Guidelines by KDIGO (Kidney Disease: Improving Global Outcomes) provide therapeutic recommendations for phosphate and calcium management but not Mg. The value of serum Mg in vascular calcification has always been underestimated and generally neglected, especially in patients on hemodialysis (HD). Dialysis patients have a higher risk of hypomagnesemia due to low Mg concentration dialysate, decreased Mg intake [9], and side effects of some drugs. Hypomagnesemia might be a pivotal factor that contributes to 2- to 5-fold more coronary artery calcification and higher all-cause mortality in maintenance dialysis patients compared with age-matched individuals [10]. Actually, several convincing animal studies and clinical trials have established a correlation between serum Mg and vascular calcification [11, 12]. However, the association between serum Mg and mortality outcomes among patients on HD remains controversial. Recognizing that individual studies might not be able to provide sufficient data on their own, we systematically reviewed original studies and performed a meta-analysis to assess the prognostic value of serum Mg levels on mortality risk in maintenance hemodialysis (MHD) patients.

Methods

Search Strategy and Selection Criteria

This meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. This study has been registered in PROSPERO with registration number CRD42019126266.

We performed a systematic literature search in EMBASE, PubMed, Cochrane Library, and Web of Science to identify relevant studies. The complete search strategy for PubMed and EMBASE is shown in online suppl. Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000510513). We also performed a manual search by using the reference lists of pertinent primary articles. Studies were considered without language restrictions. The search was last updated on June 7, 2020.

Study Selection and Data Extraction

Inclusion criteria were as follows: (1) cohort studies or clinical trials reporting the association of serum Mg with all-cause or cardiovascular mortality in MHD patients; (2) reports of hazard ratio (HR) together with 95% confidence interval (CI); or (3) sufficient data for HR extraction from Kaplan-Meier curves. A follow-up time of less than 3 months was excluded in this study. No restric-

tion was imposed on the dialysis modality or duration or sex and race of the study subjects. The primary outcome of interest was all-cause mortality and cardiovascular mortality after the initiation of HD therapy.

Two investigators (H.W. and Q.L.) independently evaluated titles and abstracts of all candidate articles based on participants, outcomes, and study designs. Full texts of selected articles were read further, and data were extracted by 2 authors (H.W. and Q.L.). Articles without consensus were evaluated by a third reviewer (L.F.), who would decide whether to include the articles. A modified version of the Newcastle-Ottawa Scale (NOS) (range 0–9) was applied to assess the quality of the included studies. Studies with scores ≥ 7 were judged as high quality. We extracted the following data from all selected studies: author, country, year of publication, number of each trial, average age, follow-up time, serum Mg cutoff value, and HR and 95% CI of all-cause mortality and cardiovascular mortality performed by univariate analysis and multivariate analysis.

Statistical Analysis

We pooled HR and 95% CI data from each study. A p value < 0.05 showed significant difference. If studies presented multiple adjusted models and categorized serum Mg, the last model and the lowest serum Mg group were utilized for merging. We further discussed the overall influence of diverse adjusted models and grouping in subgroup analysis. For articles that did not directly provide HR for mortality, we extracted data from Kaplan-Meier curves and used the method from Tierney et al. [13] to estimate the HR and 95% CI. Cochran's Q test and Higgins' I^2 statistic were taken to assess the heterogeneity of the included trials. An $I^2 > 50\%$ suggested significant heterogeneity. Subgroup analysis, sensitivity analysis, and meta-regression were applied to explore the origin of heterogeneity. Publication bias was assessed by funnel plot, Begg's rank correlation test, and Egger's linear regression test ($p < 0.05$ was considered a noteworthy publication bias). The trim and fill method [14] was applied to test and adjust for publication bias. In addition, a contour-enhanced meta-analysis funnel plot [15] was performed to predict the influence of unknown research studies on our findings. All analyses were carried out by the STATA statistical software version 12.0 (STATA, College Station, TX, USA).

Results

Study Selection

We identified 524 titles (137 in PubMed, 255 in Web of Science, 98 in EMBASE, 32 in Cochrane, and 2 in references). Of these, 20 articles were set aside for further assessment after a screening of abstracts and full-text reading. In the process of data extraction, we found 1 article on a randomized controlled experiment [16] that was unsuitable for data integration with the remaining observational studies. A study by Sakaguchi et al. [17] was excluded due to lack of HR and available Kaplan-Meier curves. We identified 2 studies [18, 19] about peritoneal dialysis that were not suitable for data merging. Adjusted

Table 1. The basic information of the included studies

References	Year	N	Study type	Country	Dialysis modality	Dialysate Mg, mmol/L	Female, %	Mean age, years	Follow-up, months	NOS
Ishimura et al. [20]	2007	515	Retrospective	Japan	HD	1	40.6	60	51	7
Tamura et al. [21]	2019	392	Prospective	Japan	HD	1	34.7	68	48	8
Markaki et al. [22]	2012	74	Prospective	Greece	HD	0.5	45	65	50	8
Matias et al. [23]	2015	206	Prospective	Portugal	HD	1	45	63.6	48	8
Ago et al. [24]	2016	399	Retrospective	Japan	HD	1	36.8	65.8	12	6
Lacson Jr et al. [25]	2015	27,544	Retrospective	North America	HD	Various	46.3	61.9	12	7
Li et al. [26]	2015	9,359	Retrospective	Multiple countries	HD	NA	43.8	63.3	60	7
Shimohata et al. [27]	2019	83	Retrospective	Japan	HD	NA	34.9	59.1	120	8
Lu et al. [28]	2020	412	Retrospective	China	HD	0.5	42.6	50.4	12	6
Kurita et al. [29]	2015	3,276	Prospective	Japan	HD	NA	38	61.7	36	8
Selim et al. [30]	2017	185	Prospective	Macedonia	HD	0.5	40.5	49.74	60	8
Wu et al. [31]	2019	169	Retrospective	China	HD	0.5	46.2	60.2	54	6
Mizuiiri et al. [32]	2019	353	Prospective	Japan	HD	1	33.4	68	36	7

NOS, Newcastle-Ottawa Scale; HD, hemodialysis; PD, peritoneal dialysis; NA, not available.

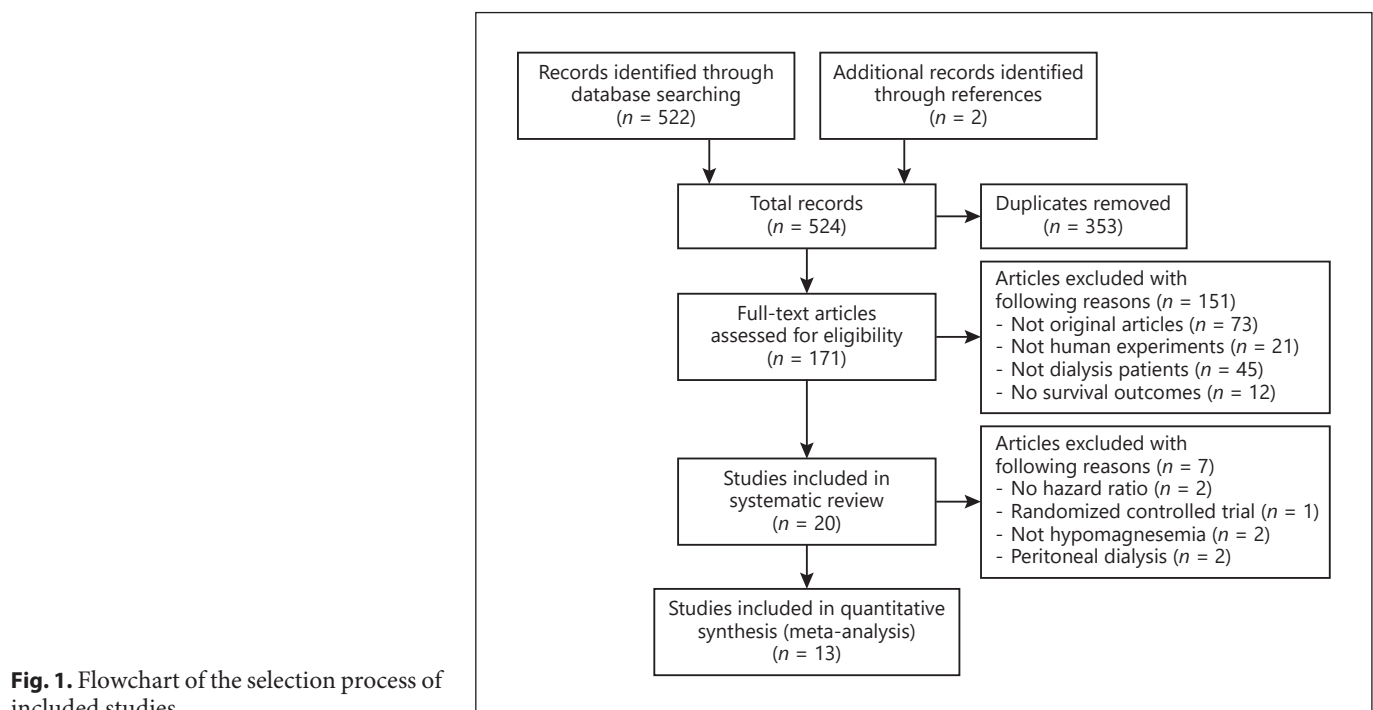


Table 2. Association between serum magnesium and all-cause and cardiovascular mortality in maintenance dialysis patients

References	All-cause mortality		Cardiovascular mortality		Serum Mg level, mmol/L
	adjusted HR (95% CI)	unadjusted HR (95% CI)	adjusted HR (95% CI)	unadjusted HR (95% CI)	
Ishimura et al. [20]	1.14 (1.02, 1.60)	NA	NA	NA	<1.1 vs. ≥1.1
Tamura et al. [21]	2.43 (0.82, 10.23)	NA	2.67 (0.64, 12.43)	NA	<1.1 vs. ≥1.2
Markaki et al. [22]	1.16 (0.34, 3.96)	NA	NA	NA	≤1 vs. >1
Matias et al. [23]	1.15 (1.02, 1.14)	NA	1.22 (1.05, 1.39)	NA	≤1.15 vs. >1.15
Ago et al. [24]	2.41 (1.47, 4.20)	2.84 (1.45, 3.43)	NA	NA	≤0.9 vs. >0.9
Lacson Jr et al. [25]	1.12 (0.92, 1.35)	1.47 (1.22, 1.79)	NA	NA	>0.80–0.95 vs. ≥1.25
Li et al. [26]	1.39 (1.23, 1.58) 1.20 (1.06, 1.36)	1.63 (1.44, 1.85) 1.30 (1.15, 1.40)	NA	NA	<0.82 vs. ≥0.9–0.98 <0.74 vs. ≥0.74–0.82
Shimohata et al. [27]	2.73 (1.07, 6.94)	2.89 (1.39, 6.06)	NA	NA	<1.0 vs. ≥1.0
Lu et al. [28]	3.53 (1.59, 7.84)	NA	4.29 (1.42, 12.91)	NA	<1.0 vs. ≥1.0
Kurita et al. [29]	1.73 (1.20, 2.50) 1.65 (1.23, 2.21)	2.38 (1.71, 3.31) 1.74 (1.29, 2.35)	NA	NA	≤0.95 vs. ≥1.03–1.88 >0.95–1.03 vs. ≥1.03–1.88
Selim et al. [30]	1.14 (0.44, 2.89) 0.95 (0.38, 2.35)	2.34 (1.26, 4.33) 0.82 (0.44, 1.51)	NA	NA	<1.1 vs. ≥1.1–1.30 >1.30 vs. ≥1.1–1.30
Wu et al. [31]	8.3 (4.26, 16.19)	9.54 (5.37, 16.96)	9.72 (3.25, 29.1)	11.21 (4.27, 29.45)	<1.0 vs. ≥1.0
Mizuiiri et al. [32]	2.17 (0.96, 5.02)	2.79 (1.84, 4.27)	2.56 (0.72, 10.36)	3.73 (2.07, 6.98)	<1.0 vs. ≥1.0

HR, hazard ratio; CI, confidence interval; NA, not available.

HRs and 95% CIs were not provided in 2 articles [20, 21], and we, therefore, extracted data from the Kaplan-Meier curves. Finally, 13 candidate articles [20–32] were incorporated into quantitative synthesis (meta-analysis). The flowchart is shown in Figure 1.

Study Characteristics

The included articles were published between 2007 and 2020, involving 42,967 patients on HD. The characteristics of the included studies are shown in Table 1.

A total of 13 observational studies were eligible for data merging, including 6 prospective cohort studies and 7 retrospective studies. The average age of participants in included studies ranged from 49.3 to 68 years. The mean follow-up ranged from 12 to 120 months. All the studies examined the relationship between serum Mg levels and all-cause mortality among HD patients, with 5 [21, 23, 28, 31, 32] also evaluating the association between serum Mg and cardiovascular mortality. All the studies calculated HRs by multivariate analysis, and 8 [24–27, 29–32] also used univariate analysis. Catego-

rized serum Mg concentration was provided in 3 studies [26, 29, 30]. We selected the lowest serum Mg group to pool HRs. For detailed information about HRs and grouping, see Table 2.

The NOS was applied to assess the quality of included studies. A total of 10 studies were of high quality (≥7 score), and 3 were of moderate quality (4–7 score). The NOS grade for each included study is shown in online suppl. Table 2.

Association of Serum Mg with All-Cause Mortality

Our merged results of interest, the adjusted/unadjusted HRs and 95% CIs about the correlation between serum Mg and all-cause mortality, are reported in Figure 2. Among the 13 included studies, 8 indicated that a lower serum Mg level was an independent risk factor for all-cause mortality ($p < 0.05$) [20, 23, 24, 26–29, 31], and 5 studies did not reach statistical significance [21, 22, 25, 30, 32]. After pooling, our findings showed that compared with higher serum Mg groups, lower serum Mg levels increased all-cause mortality among HD patients (adjusted

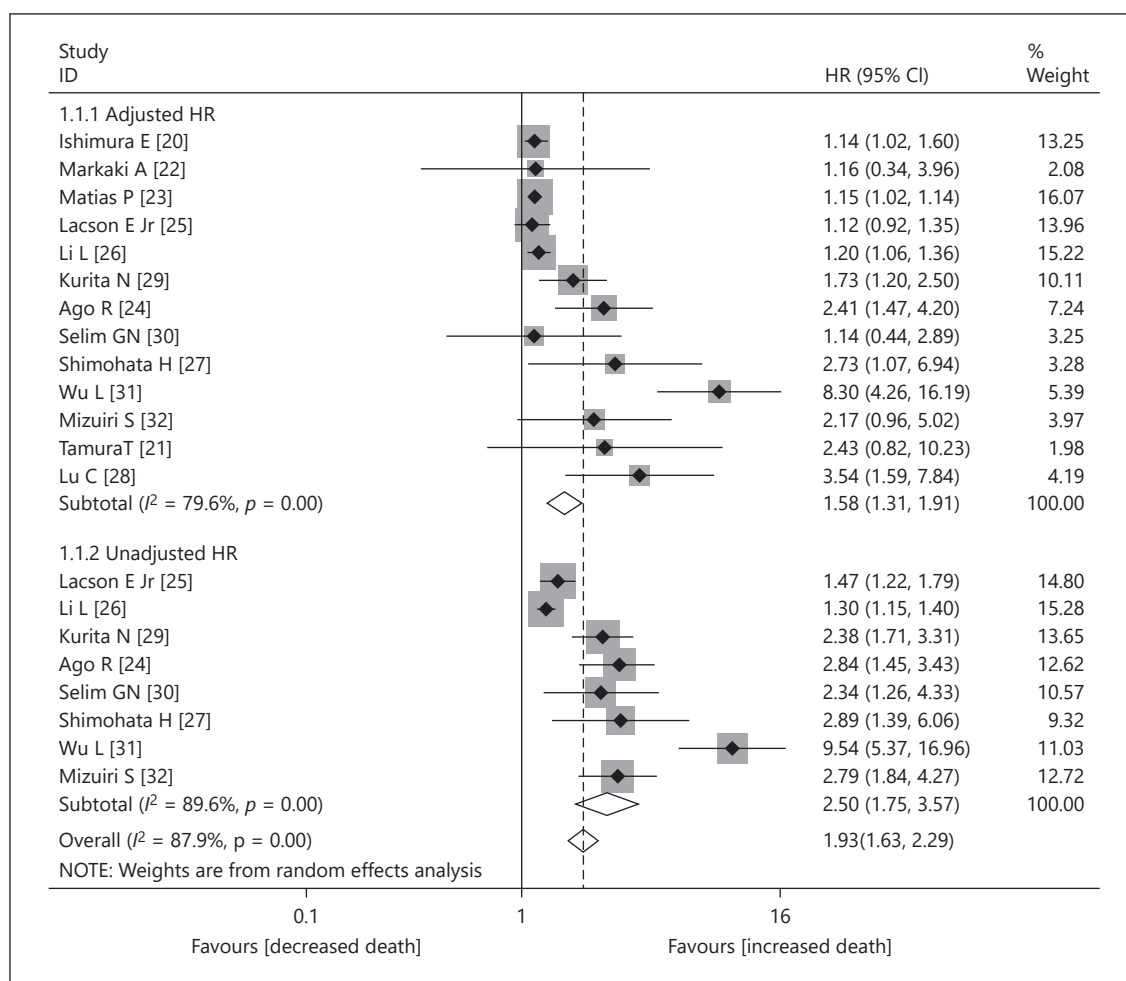


Fig. 2. The association between serum Mg levels and all-cause mortality among patients on dialysis (low vs. high Mg groups).

HR 1.58 [95% CI: 1.31–1.91] and unadjusted HR 2.5 [95% CI: 1.75–3.57]).

Interstudy heterogeneity was found ($I^2 = 79.6\%$, $p < 0.001$). To assess the heterogeneity, we performed subgroup analysis. We found that difference in age stratification and study area could partly explain the heterogeneity (online suppl. Table 3). Meta-regression also suggested that studies in different countries contributed to 29.8% of the observed heterogeneity ($p = 0.046$) (online suppl. Fig. 1). In the sensitivity analysis, the overall estimate of effect did not change meaningfully after excluding 1 article at a time (online suppl. Fig. 2). The I^2 value dropped to 48.1% after the study by Wu et al. [31] was excluded, with a materially unchanged result (adjusted HR 1.33 [95% CI: 1.16–1.52, $p = 0.01$]).

As cutoff values of low serum Mg concentration differed from each study, we further analyzed the effects of

different serum Mg concentration on overall survival. The results showed that concentrations of Mg ≤ 0.75 mmol/L (HR 1.20 [95% CI: 1.06–1.36]), Mg ≤ 0.9 mmol/L (HR 1.59 [95% CI: 1.02–2.49]), and Mg ≤ 1.1 mmol/L (HR 1.89 [95% CI: 1.37–2.61]) were risk factors for all-cause mortality, except Mg > 1.1 mmol/L, which did not reach statistical significance (HR 0.95 [95% CI: 0.38–2.36, $p > 0.05$]) (Fig. 3). It seems that a serum Mg concentration of ≤ 1.1 mmol/L might be the vigilant cutoff value.

Influence of Serum Mg Levels on Cardiovascular Mortality Risk

We included 5 studies [21, 23, 28, 31, 32] in the evaluation of cardiovascular mortality. We found that a lower serum Mg level increased cardiovascular mortality among patients receiving dialysis (adjusted HR 3.08 [95% CI:

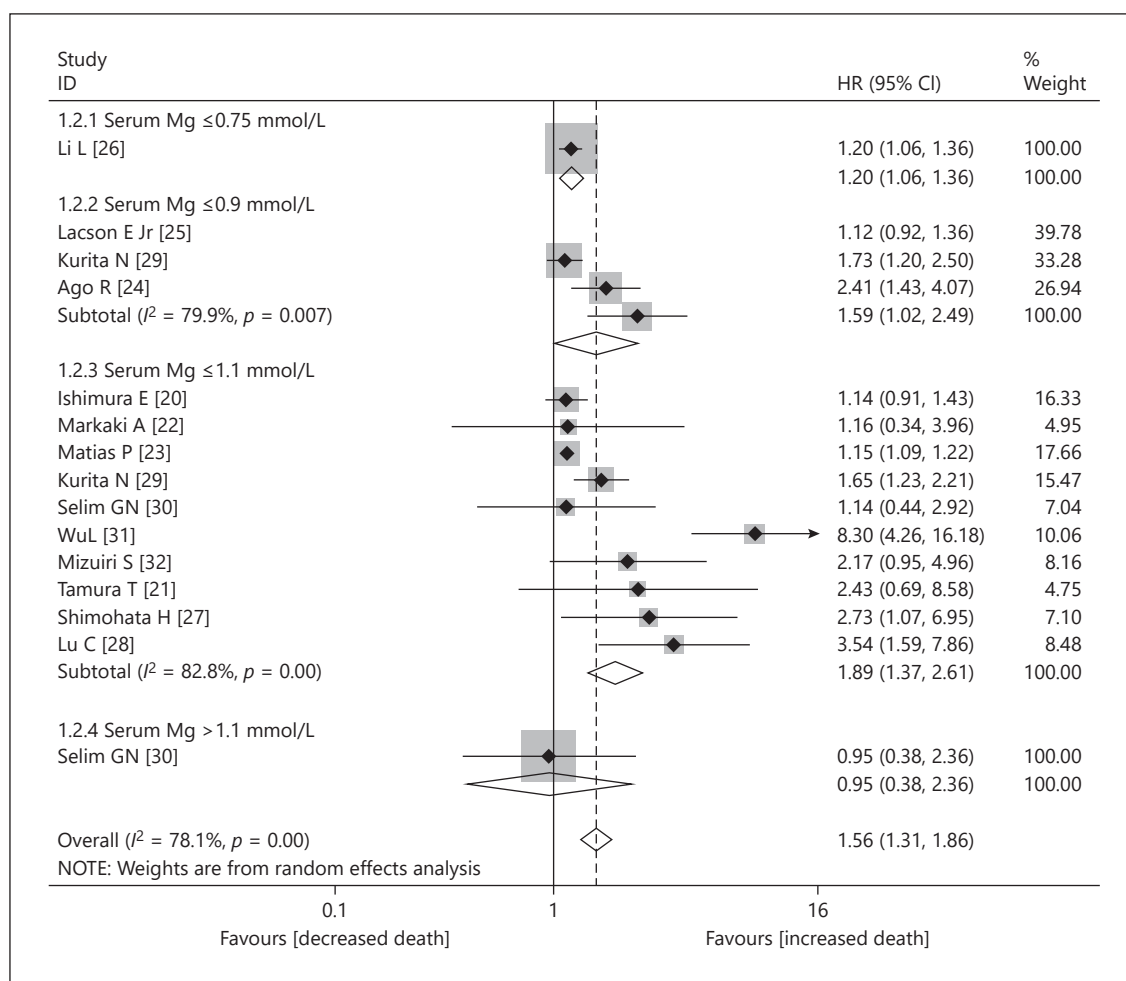


Fig. 3. Subgroup analysis by Mg cutoff level on all-cause mortality (low vs. high Mg groups).

1.27–7.50], $p < 0.001$, and unadjusted HR 6.05 [95% CI: 2.07–17.65], $p < 0.001$) (Fig. 4).

Publication Bias

Publication bias was evident in the asymmetric funnel plot and Egger's test ($p = 0.009$) (Fig. 5 and online suppl. Fig. 3). Subsequently, we used the trim-and-fill method to adjust for publication bias. After the addition of 4 articles to this model, the adjusted HR did not change significantly (HR 1.32 [95% CI: 1.06–1.62, $p = 0.01$]) (Fig. 5 and online suppl. Fig. 4), indicating that existing publication bias had little effect on our results. Furthermore, we performed the contour-enhanced meta-analysis funnel plot to predict the influence of unknown research on our findings (online suppl. Fig. 5). We found that future research will most likely have a meaningful impact on current results; thus, more investigations are essential in the future.

Discussion

Mg^{2+} plays a key role in the maintenance of homeostasis, and previous studies have reported the prognostic value of serum Mg levels in patients receiving dialysis. However, the results of those studies remain inconsistent. We targeted the HD population, which has both a high prevalence of serum Mg deficiency and a high early mortality rate, and performed a meta-analysis to obtain a more comprehensive estimation of mortality risk associated with serum Mg levels.

After data merging, we found that lower serum Mg level was associated with increased all-cause mortality and cardiovascular mortality in HD patients, despite 5 studies that did not reach statistical significance. These findings are consistent with the results found for peritoneal dialysis patients [18, 19], revealing that low Mg con-

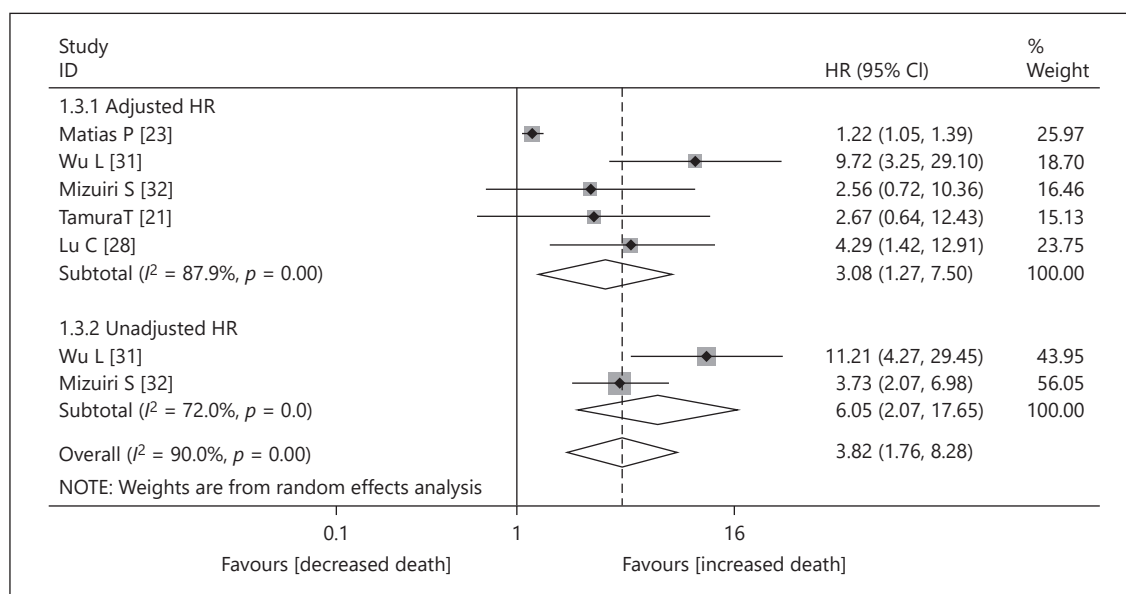


Fig. 4. The association between serum Mg levels and cardiovascular mortality risk (low vs. high Mg groups).

centrations have negative effects on both HD and PD patients. It should be noted that heterogeneity existed among the included studies, and differences in age stratification and study area could partly explain the heterogeneity after subgroup analysis and meta-regression. Importantly, subgroup analysis showed that the pooled results from studies in the Europe area did not reach statistical significance, indicating that our findings might be more practical in Asia. Studies have documented international variation in prevalence, patient survival, and patterns of medical practice related to dialysis [33, 34]; thus, the practicability and feasibility of our results in different countries also need to be further explored. Our findings primarily depended on baseline Mg measurement. In fact, serum Mg concentrations in HD patients tend to decrease slightly with 0.011 mmol/L/year [16] due to reduced dietary intake, dialytic clearance, and concomitant medications. The risk of variation in Mg levels has been largely ignored in HD patients. A study of 169 MHD patients reported that a group with high variation in Mg ($\Delta\text{Mg} \geq 0.149$ mmol/L) had a higher all-cause mortality than the group with middle variation ($0.114 \leq \Delta\text{Mg} < 0.149$ mmol/L), despite multivariate Cox regression analysis indicating that serum Mg variability was not an independent factor for all-cause mortality or cardiovascular mortality [31]. Further investigation of the relationship between Mg variability and mortality is imperative.

The warning threshold for serum Mg concentration in mortality prediction is difficult to determine. A study

by Sakaguchi et al. [17] revealed a J-shaped relevancy between all-cause mortality and serum Mg concentrations in HD patients, with a “sweet spot” around 1.2 mmol/L. Similar findings were determined in a study of patients from the United States that indicated that the best survival was observed for serum Mg levels of 1.25 mmol/L [25]. Subgroup analysis in our study suggested that serum Mg concentration ≤ 1.1 mmol/L might be the vigilant cutoff value. Notably, a meta-analysis performed by Angkananard et al. [35] concluded that hypermagnesemia ($\text{Mg} \geq 1.05$ mmol/L) was correlated with increased all-cause mortality, but this was not observed for hypomagnesemia. Although this finding was limited to patients with chronic heart failure not on dialysis, we should recognize that excessive Mg concentration was also likely to pose a risk, especially in an elderly population. In fact, extreme concentrations of serum Mg (<0.7 mmol/L or >1 mmol/L) is a common ionic disorder with high risk of adverse clinical outcomes. Hypermagnesemia is speculated to cause excessive inhibition of parathyroid hormone and adverse effects of other mineral metabolism (osteomalacia) [36], while hypomagnesemia can lead to endothelial dysfunction and induce cardiac arrhythmias. Therefore, addressing the issue of when and how to start Mg supplementation is an urgent need.

Clearly, serum Mg concentrations are affected by dialysis prescription to a large extent. More recently, a study reported that 33% of patients developed hypomagnesemia

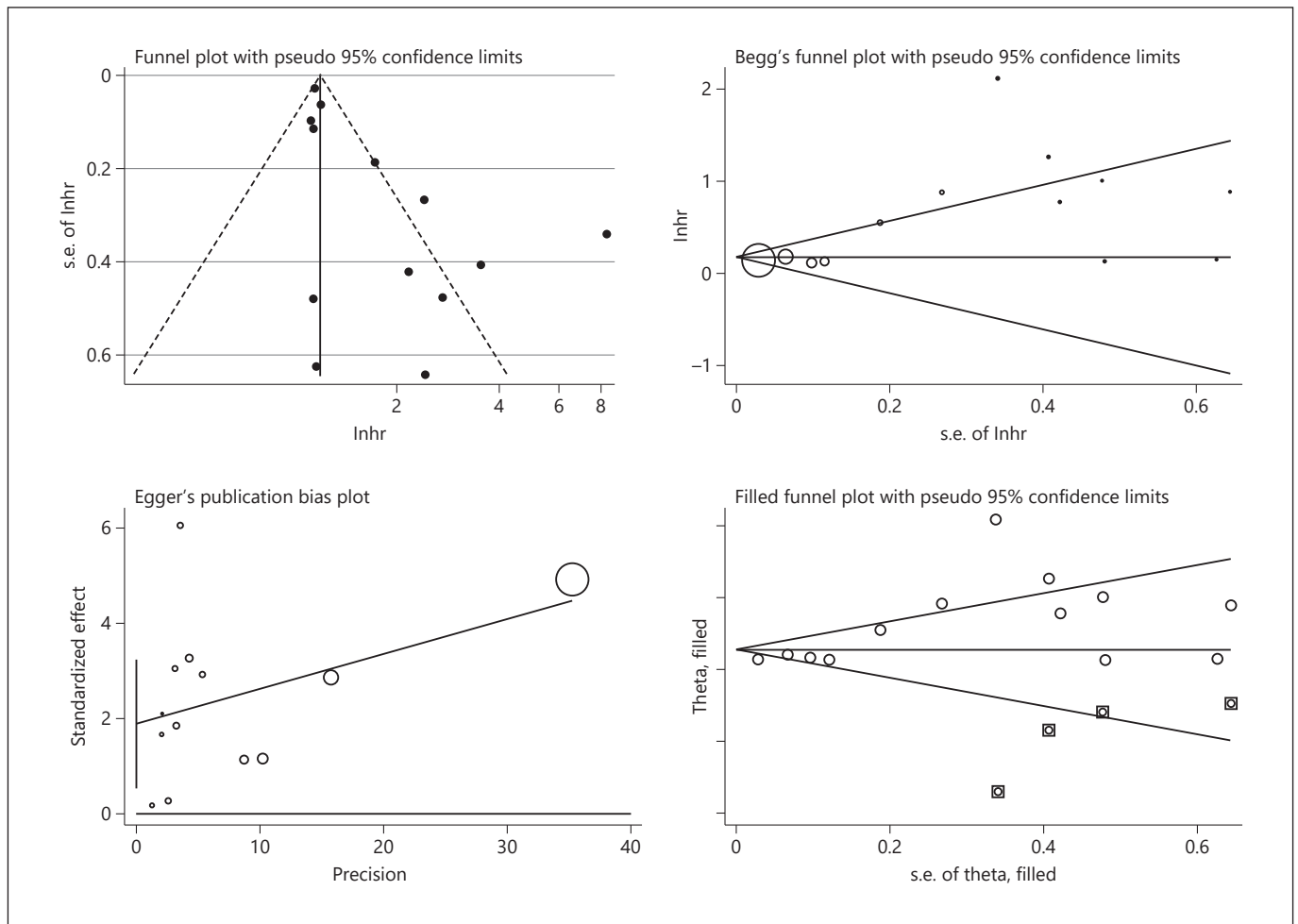


Fig. 5. Funnel plot of the association between serum Mg and all-cause mortality. **a** The funnel plot with pseudo 95% confidence intervals (CIs). **b** Begg's funnel plot with pseudo 95% CIs. **c** Egger's publication bias plot. **d** Trimmed and filled funnel plot with pseudo 95% CIs.

mia with dialysate Mg of 0.25 mmol/L, while only 5% of patients exposed to dialysate Mg of 0.5 mmol/L developed hypomagnesemia [37]. Importantly, interactions between dialysate Mg concentrations and other dialysate constituents should be recognized, especially potassium content. Low Mg dialysate could raise risk of arrhythmia and myocardial infarction associated with low potassium dialysate, considering the effect of hypomagnesemia on the risk of hypokalemia by promoting intracellular potassium shifts [38]. Therefore, the risk of fatal arrhythmia caused by the overlaying of hypokalemia and hypomagnesemia must be avoided. Given the adverse effects of hypomagnesemia, hypermagnesemia, and hypokalemia, higher Mg dialysate levels of 0.5–1 mmol/L are recommended, which is comparable with the dialysate Mg concentrations in our included studies. Additionally, proton

pump inhibitors are believed to have the potential to lower serum Mg concentrations in HD patients with nutritional issues [37], which should also be brought to our attention. So, what is the optimal dose for Mg supplementation? Studies have showed that Mg supplementation improved flow-mediated dilatation and enhanced exercise tolerance (365 mg/d) [39] as well as decreased carotid intima-media thickness in HD patients (610 mg every other day) [40]. Moreover, results from meta-analysis supported that increasing dietary Mg intake (per 100 mg/day increment) was related to reduced risk of ischemic stroke [41], heart failure, and all-cause mortality [42]. However, a special Mg supplement guideline aimed at the dialysis population is essential due to differing Mg^{2+} absorption and excretion abilities of dialysis patients from those of healthy subjects. Meanwhile, Mg concentration

must be carefully monitored during interventions because the safety of high Mg levels has not yet been proven.

Mg acts as a calcification inhibitor through multiple molecular mechanisms [43]. First, the entry of calcium into the cells is inhibited because calcium channels are antagonized by Mg^{2+} [44]. Second, Mg can inhibit the transformation from amorphous Ca/P to a hydroxyapatite forming dissolvable whitlockite [45, 46]. Third, via transient receptor potential melastatin 7, Mg^{2+} restores the balance between expression of calcification promoters and inhibitors by preventing the loss of BMP-7 and suppressing expression of osteogenic transcription factors (BMP-1, RUNX-2, and SRY-box9) [11, 47], preventing vascular smooth muscle cell from osteoblastic conversion and calcification. Furthermore, it has been certified that Mg^{2+} could act on the CaSR and further inhibit vascular smooth muscle cell calcification [48]. Therefore, dialysis patients with low serum Mg concentrations have a higher risk of vascular calcification and cardiovascular events.

Our study was restricted by several factors. First, significant heterogeneity was observed among the included studies, which was partly explained by differences in the average age of the study population as well as study geographic location. Second, potential residual confounding could not be excluded because adjusted HRs from each study were confounded due to the possibility that adjustments were for different covariates. Third, only baseline serum Mg was tested, and the fact that Mg levels might change over time was ignored. Finally, the cutoff value of low Mg levels was not consistent which might also cause heterogeneity. In the future, randomized trials should investigate the limiting cutoff values of Mg concentration in predicting mortality and define the effects of Mg supplementation among patients on dialysis.

In summary, our meta-analysis of observational studies shows that a lower serum Mg level is associated with higher all-cause mortality and higher cardiovascular mortality in patients receiving HD. These findings could be of clinical significance in that the serum Mg levels could be a predictive factor for mortality among HD patients and a treatment strategy for Mg supplementation.

Acknowledgements

The authors thank Prof. Bin Wang from the Institute of Economics of Jinan university for providing help for statistical analysis.

Statement of Ethics

This study did not require approval because it does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest to disclose.

Funding Sources

This work was supported by the Clinical Engineering of Blood Purification in Guangdong Province (507204531040).

Author Contributions

Research idea and study design: H.W., Q.L., and L.F.; data collection: D.Z., X.C., B.G., B.H., and C.Y.; data analysis: H.W. and Q.L.; manuscript writing: H.W.; language adviser: Y.L., B.K., and B.H.; manuscript modification: L.Y. and F.L.

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