Associations between the serum magnesium and all-cause or cardiovascular mortality in chronic kidney disease and end-stage renal disease patients

A meta-analysis

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Abstract

Background: Some studies have found that hypomagnesemia is associated with vascular calcification, atherosclerosis, and cardiovascular disease, which may lead to increased mortality in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) who need to maintain hemodialysis (HD). However, the conclusion of these studies remain controversial.

Methods: Relevant literature was retrieved from the database of Cochrane library, PubMed, EMBASE, and CNKI until December 2020, without any language restrictions. The data was analyzed using the Stata 12.0 software.

Results: A total of 31 studies were included, involving 205436 participants. The results showed that after multivariable adjusted, hypomagnesemia was significant associated with the risk of all-cause mortality in patients with CKD and end-stage renal disease (ESRD) (hazard ratios [HR] 1.955; 95% confidence interval (95% CI) 1.511-2.528; $P = .000$; hypomagnesemia vs normal magnesium or hypermagnesemia). In contrast, in patients with CKD and ESRD, hypermagnesemia was negatively correlated with all-cause mortality (HR 0.873; 95% CI 0.793-0.960; $P = .005$) (per unit increase). Moreover, in the adjusted model, it was observed that hypermagnesemia was significantly associated with a reduced risk of cardiovascular death (HR 0.598; 95% CI 0.094-1.102, $P = .020$). In addition, subgroup analysis found that hypomagnesemia was closely related to the increase of all-cause mortality in HD patients (HR 1.799; 95% CI 1.375-2.354; $P = .000$) (hypomagnesemia vs normal magnesium or hypermagnesemia).

Conclusion: Our results show that hypomagnesemia is significantly associated with cardiovascular and all-cause mortality in maintenance HD patients. Further studies should be conducted to evaluate the benefits of magnesium correction in maintenance dialysis patients with hypomagnesemia.

Abbreviations: 95% CI = 95% confidence interval, CKD = chronic kidney disease, ESRD = end-stage renal disease, HD = hemodialysis, HR = hazard ratios, OR = odds ratio, PD = peritoneal dialysis.

Keywords: all-cause mortality, cardiovascular events, maintenance hemodialysis, meta-analysis, serum magnesium

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1. Introduction

Magnesium ion is one of the most abundant cations in cells and in the whole body.[1] This inorganic ion plays an important role in many physiological functions of human cells, including DNA and protein synthesis, glucose and fat metabolism, oxidative phosphorylation, neuromuscular excitability, enzyme activity, vascular tension regulation, heart rhythm, and thrombosis.[2,3] In addition, the level of serum magnesium also has a great influence on the function of the cardiovascular system.[4]

Studies have reported that low serum magnesium levels can accelerate vascular calcification and atherosclerosis, both of which can lead to cardiovascular disease and may increase the risk of sudden cardiac death.[5] Moreover, a large number of prospective observational studies and meta-analysis results show that in the general population, serum magnesium levels are negatively correlated with cardiovascular events.[6–8]

Cardiovascular disease is one of the leading causes of death in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD).[9] The kidney plays an important role in maintaining the homeostasis of serum magnesium.[10] In patients with moderate CKD (stages 1-3), the increased excretion of magnesium ions through urine compensates for the loss of renal

function. Therefore, the content of magnesium remains within the normal range. In more advanced CKD patients (stage 4-5), the renal compensation mechanism becomes inadequate. For CKD patients, mild to moderate elevated serum magnesium levels may have potential benefits, but may also have harmful side effects. However, hypermagnesemia in dialysis patients is associated with a slower process of vascular calcification.[11] Researchers have conducted several observational studies to evaluate the relationship between serum magnesium levels in patients with chronic kidney disease and cardiovascular disease, cardiovascular events, and mortality.[11–15] However, the results of these studies do not have a unified conclusion, because many of these studies have shown that serum magnesium levels are negatively correlated with cardiovascular mortality, but there are also other studies that show that there is no significant difference between serum magnesium levels and mortality in CKD or ESRD patients. The relevance. Therefore, our purpose of conducting this study is to summarize the results of the existing relevant literature and conduct a meta-analysis to assess the relationship between serum magnesium levels and mortality in patients with CKD and ESRD.

2. Materials and methods

2.1. Search strategy

We conducted a comprehensive search of the literature in the database, identified relevant literature and extracted data for analysis to determine the relationship between serum magnesium, hypomagnesemia or hypermagnesemia and mortality in maintenance hemodialysis (HD) patients. These studies were completed during the period from the start of the study to December 2020 by searching the PubMed, EMBASE, Web of Science, CNKI, Wanfang, and Cochrane Central Register of Control Trials (CENTAL) databases. The key words are as follows: "serum magnesium or hypermagnesemia or hypomagnesemia", "mortality or death", and "chronic kidney disease or CKD or end-stage renal disease or (ESRD) or dialysis or HD or peritoneal dialysis". In addition, we also manually searched the references of established studies and review articles. The literature included in our study also included abstracts from academic conferences on kidney disease.

2.2. Inclusion and exclusion criteria

Inclusion criteria include: studies reporting all-cause or cardiovascular-related mortality in patients with serum magnesium and CKD and ESRD, primarily including HD and peritoneal dialysis patients; cohort studies, including retrospective and prospective cohort studies; and reports with 95% confidence intervals (95% CI) or sufficient data to calculate these numbers: advantage ratio (odds ratio [OR]), relative ratio, or risk ratio (hazard ratios [HR]), relative ratio, or risk ratio (HR). The criteria for excluding the study include the following: studies with unreported cardiovascular death or all-cause mortality, and follow-up periods of less than 3 months. We were interested in baseline serum magnesium levels. There were 3 main forms of exposure: serum magnesium levels, hypomagnesemia, and hypermagnesemia. HRs for serum magnesium were collected from continuous and dichotomous variables, respectively. Serum magnesium (per unit increment) was used as a continuous variable to measure the HRs of serum magnesium. Taking serum magnesium as a dichotomous variable, the HRs of serum magnesium was

calculated by hypomagnesemia group vs normal magnesium group or hypomagnesemia group vs hypermagnesemia group according to the type of magnesium in each study. The main interesting result is the risk assessment of all-cause and cardiovascular mortality through serum magnesium.

2.3. Data extraction

In this study, 2 researchers independently evaluated each study and recorded eligibility, quality, and results. The different opinions were resolved through discussions with the investigators. The third investigator provided arbitration in the event of a dispute. The following basic study information was collected: first author, year of publication, country, number of participants, study design, follow-up time, and outcomes.

2.4. Evaluations of statistical associations

We calculated a combined estimate of the relative ratio of and 95% compliance extracted from the included study, or calculated from the data, to assess the relationship between all-cause or cardiovascular mortality and serum magnesium level in patients with CKD and ESRD. The quality of all research was assessed with reference to the Newcastle–Ottawa Scale. The research evaluation criteria were mainly divided into 3 aspects: measurement results, comparability, and queue selectivity. These aspects were further categorized into the number of stars, in a descending order, with grade A = 7 to 10 stars, grade B = 4 to 6 stars, and grade C = <3 stars.[16] During this process, in case of a conflict, negotiation was made to resolve the dispute. We extracted various risk assessments from multiple data such as OR and HR for each of the included studies. The ORS was used to crudely assess correlations between different studies. Both unadjusted risk estimates and adjusted risk estimates were aggregated into the meta-analysis. Unadjusted and adjusted HR or OR are collected. The unadjusted mean of the rough model is not modified by any other factors, whereas the adjusted HR means that other factors in the model have been adjusted. I^2 test and chi-square-based test were applied to analyze the heterogeneity among the included articles. The range of heterogeneity was as follows: extreme = 75% to 100%; large = 25% to 50%; and moderate = <25%. The fixed-effects model was generally used to evaluate the research content because I^2 was <50%. A random effect model was used whenever the value was >50%.[17] Any publication bias was assessed by using the Begg test and the Egger test. Sensitivity analysis was applied to analyze large heterogeneity studies and to find the source of heterogeneity. The data from the individual studies were pooled and analyzed using the Stata 12.0 software (Stata Corporation, College Station, TX).

The procedures followed were in accord with the ethical standards of the committee on human experimentation of Renmin Hospital of Wuhan University and in accord with the Declaration of Helsinki and its revisions. In addition, oral informed consent was obtained from subjects.

3. Results

3.1. Search strategy and characteristics of studies

According to the above-mentioned retrieval methods, 1019 relevant studies were selected for the analysis. The flow chart of the screening process for the studies included in this meta-analysis
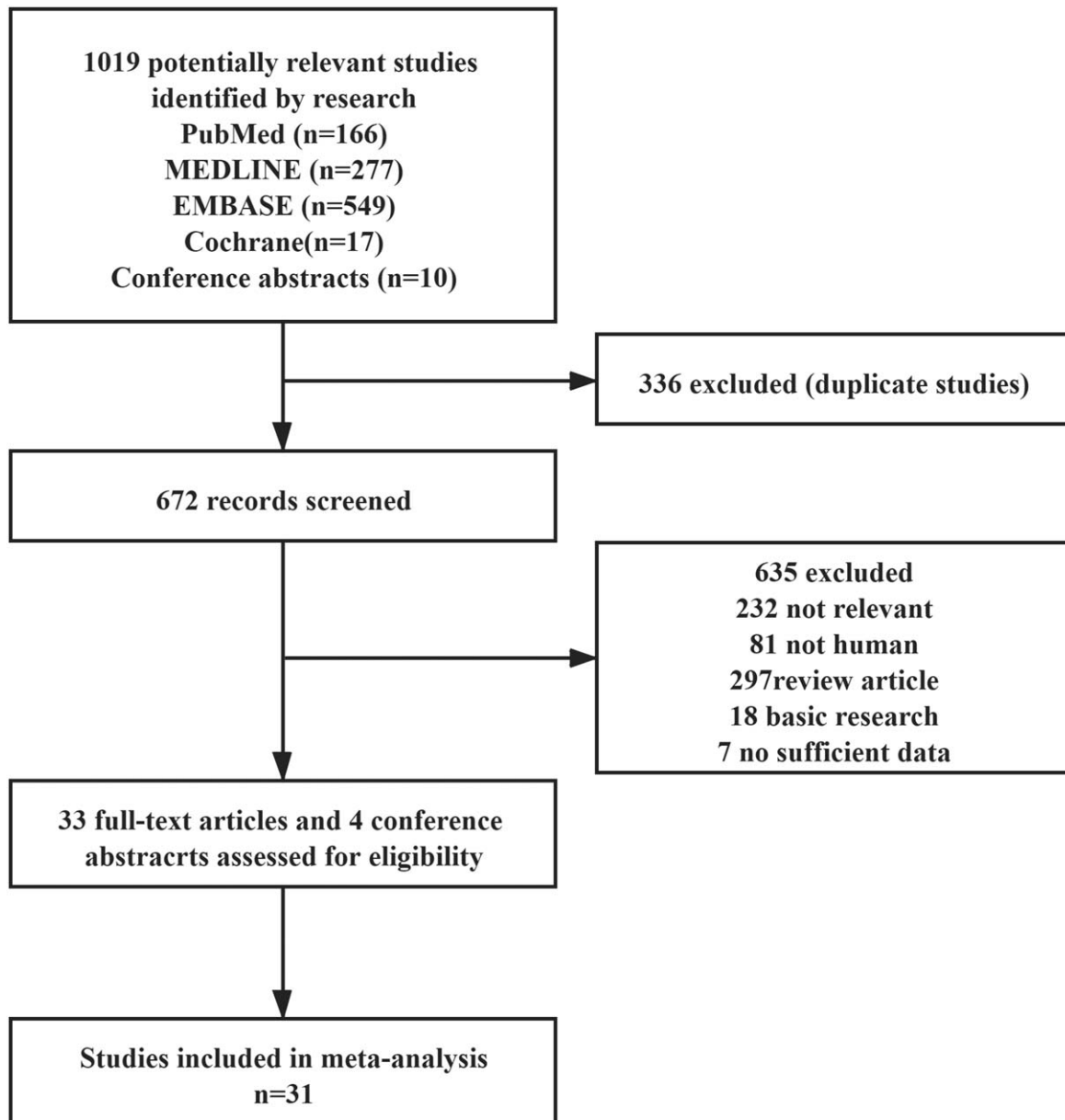
Figure 1. Flowchart of selection of studies.

is shown in Figure 1. We deleted 336 duplicate records by screening the titles. After skimming the titles, abstracts, and reviewing the full-text content, 672 studies were excluded due to the lack of available data or the non-RCT nature of the study, among other reasons. We then carefully read the full text of each of the remaining 37 studies. Finally, 13 studies involving 205,436 patients met the inclusion criteria.[11,13,14,18–45] As shown in Table 1, the studies that met the inclusion criteria were all conducted between 2007 and 2020, involving 205,436 patients. The sample size ranges from 50 to 142,555. There are 16 studies from Asia, 12 from Europe and 3 from the United States. Four studies investigated people with disease, including patients with CKD, and 20 of the included studies were studies that included patients on HD. There were also 5 studies of patients on peritoneal dialysis (PD) and 2 studies that included both HD and

PD patients. Sixteen studies conducted a risk assessment of the relationship between magnesium levels and all-cause mortality, 15 studies reported on the association between serum magnesium levels and all-cause and cardiovascular mortality.

3.2. Quality assessments

As per the description given in Tables 1 and 2, all references in the meta-analysis belonged to grade A. Therefore, it can be concluded that this study involved the analysis of high-quality literature.

3.3. All-cause and cardiovascular mortality
3.3.1. Relationship between serum magnesium levels and all-cause mortality. Twelve studies are listed in Table 3, reporting unadjusted HR and OR between hypomagnesemia and

Table 1

Characteristics of the eligible studies in this meta-analysis.

Study	Year	Country	N, total	Age (yrs)	Follow-up time	Retrospective/ prospective	Patients	Outcome	NOS score
Ishimura et al[18]	2007	Japan	515	60±12	51 mo	Retrospective	HD	All-cause and cardiovascular mortality	7
Markaki et al[19]	2012	Greece	74	65±15	50 mo	Prospective	HD and PD	All-cause mortality	6
Ortega et al[20]	2013	Spain	70	64±13	2 yrs	Prospective	CKD	All-cause and cardiovascular mortality	6
Broek et al[21]	2013	Germany	761	63±14	3 yrs	Prospective	HD and PD	All-cause and cardiovascular mortality	7
Laecke et al[22]	2013	Belgium	1650	57.4±17.3	5.1 yrs	Prospective	CKD	All-cause mortality	7
Lacson et al[11]	2014	Germany	27,544	61.9±15.0	12 mo	Retrospective	HD	All-cause mortality	7
Fein et al[23]	2014	United States	62	55±16	10.8 yrs	Retrospective	PD	All-cause mortality	6
Sakaguchi et al[14]	2014	Japan	142,555	66.0±12.5	12 mo	Retrospective	HD	All-cause mortality	6
Li et al[24]	2015	United States	9359	63.3±14.9	5 yrs	Retrospective	HD	All-cause mortality	7
de Roij van Zuijdewijn et al[25]	2015	The Netherlands	714	64.1±13.7	36 mo	Retrospective	HD	All-cause and cardiovascular mortality	7
Matias et al[26]	2015	Portugal	206	63.6±14.3	48 mo	Prospective	HD	All-cause and cardiovascular mortality	7
Garagarza et al[27]	2015	Portugal	605	69.9	81.7 mo	Prospective	HD	All-cause mortality	6
Kurita et al[28]	2015	Japan	3276	61.7±12.5	3 yrs	Prospective	HD	All-cause mortality	6
Yang et al[13]	2016	China	10,692	56±16	60 mo	Retrospective	PD	All-cause mortality	7
Cai et al[29]	2016	China	253	58±16	29 mo	Retrospective	PD	All-cause and cardiovascular mortality	7
Ago et al[30]	2016	Japan	399	65.86±11.8	12 mo	Retrospective	HD	All-cause mortality	7
Hughes et al[31]	2016	United Kingdom	1306	67.7	3.07 yrs	Prospective	CKD	All-cause mortality	7
Lv et al[34]	2016	China	93	65.3±14.7	5 yrs	Retrospective	HD	All-cause and cardiovascular mortality	6
Ferrè et al[32]	2017	United States	306	46.8±69.0	12.3 yrs	Retrospective	CKD	All-cause and cardiovascular mortality	7
Schmaderer et al[35]	2017	Germany	50	67.9	3 yrs	Prospective	HD	All-cause mortality	7
Sato et al[36]	2017	Japan	253	68.8±12.3	4 mo	Retrospective	HD	All-cause and cardiovascular mortality	6
Selim et al[33]	2017	Republic of Macedonia	185	49.74±14.71	5 yrs	Prospective	HD	All-cause and cardiovascular mortality	7
de Francisco et al[37]	2017	Spain	2242	68.1	6 mo	Retrospective	HD	All-cause mortality	7
Zhang et al[38]	2017	China	92	73.92±10.73	5 yrs	Retrospective	HD	All-cause mortality	7
Ye et al[39]	2018	China	402	49.3±14.9	49.9 mo	Prospective	PD	All-cause and cardiovascular mortality	7
Li et al[40]	2019	China	446	53.52±15.21	3 yrs	Retrospective	HD	All-cause and cardiovascular mortality	6
Lu et al[41]	2019	China	413	50.4±14.3	12 mo	Retrospective	HD	All-cause and cardiovascular mortality	6
Mizuiri et al[42]	2019	Japan	215	73	3 yrs	Retrospective	HD	All-cause mortality	6
Wu et al[43]	2019	China	169	60.20±15.64	37 mo	Prospective	HD	All-cause and cardiovascular mortality	7
Ogawa et al[44]	2020	Japan	148	56.4±10.5	6 yrs	Prospective	HD	All-cause mortality	7
Guan et al[45]	2020	China	381	56.1±14.2	6.5 yrs	Prospective	PD	All-cause and cardiovascular mortality	7

CKD = chronic kidney disease, HD = hemodialysis, N = number, NOS = Newcastle–Ottawa Scale, PD = peritoneal dialysis.

all-cause mortality (HR calculated based on binary variables, hypomagnesemia compared to normal or hypermagnesemia). Our results demonstrated that hypomagnesemia is significantly associated with increased all-cause mortality in patients with CKD (HR 1.955; 95% CI 1.511-2.528, P = .000, Fig. 2). Thirteen studies reported the relationship between adjusted HR and OR and hypomagnesemia and all-cause mortality. Our results show that hypomagnesemia is associated with an increased risk of all-cause death after multivariate adjustment (HR 1.530; 95% CI 1.280-1.829, P = .000, Fig. 2). In patients with CKD and ESRD, 6 studies reported unadjusted HRs between hypermagnesemia and all-cause mortality (HR calculated on continuous variables, per unit increase). As shown in Figure 3, our results show that hypomagnesemia is significantly associated with a reduced risk of all-cause mortality (HR 0.326; 95% CI 0.137-0.778, P = .012). Eight studies have reported the relationship between adjusted hypermagnesemia and all-cause mortality, and our data showed a significant association between hypomagnesemia and a decreased risk of all-cause mortality (HR 0.873; 95% CI 0.793-0.960; P = .005, Fig. 3). We also performed a subgroup analysis and the results suggested a significant correlation between hypomagnesemia and increased mortality in HD patients (HR 1.799; 95% CI 1.375-2.354; P = .000, Fig. 4A) (HR was calculated from dichotomous variables, comparing

between hypermagnesemia and normomagnesemia or hypomagnesemia). In addition, there was significant association between hypomagnesemia and reduced all-cause mortality in HD patients (HR 0.697; 95% CI 0.540-0.900; P = .006; Fig. 4B), (HR was calculated from continuous variables, comparing between hypomagnesemia and normomagnesemia or hypermagnesemia). CKD and PD cannot calculate HR due to limited data. Finally, a subgroup analysis of the association between serum magnesium levels and all-cause mortality was performed, as shown in Table 4. The subgroup analysis was based on location (Asia and non-Asia), age (≥60 and <60), follow-up time (>5 years and <5 years), participants' tendency (chronic kidney disease and dialysis) and method quality (score <7 and ≥7) and study design (prospective and retrospective). In conclusion, there was a significant association between serum magnesium and all-cause mortality in all subgroups (Table 4).

3.3.2. Relationship between serum magnesium levels and cardiovascular mortality. Table 3 shows that 3 studies reported a negative correlation between serum magnesium and cardiovascular mortality (HR calculated on dichotomous variables), Unadjusted HRs, hypomagnesemia was negatively correlated with cardiovascular mortality (HR 1.403; 95% CI 0.077-25.607, P = .819, Fig. 5). In addition, 5 studies reported the association

Table 2

Quality evaluation of the included studies.

Study	Queue selection	Comparability	Result measurement	Level of quality
Ishimura et al[18]	★★★★	★	★★★	7
Markaki et al[19]	★★★	★	★★★	6
Ortega et al[20]	★★★	★	★★★	6
Broek et al[21]	★★★★	★	★★★	7
Laecke et al[22]	★★★★	★	★★★	7
Lacson et al[11]	★★★★	★	★★★	7
Fein et al[23]	★★★★	★	★★★	6
Sakaguchi et al[14]	★★★★	★	★★	6
Li et al[24]	★★★★	★	★★★	7
de Roij van Zuijdewijn et al[25]	★★★	★	★★★	7
Matias et al[26]	★★★★	★	★★★	7
Garagarza et al[27]	★★★	★	★★★	6
Kurita et al[28]	★★★	★	★★★	6
Yang et al[13]	★★★	★	★★★	7
Cai et al[29]	★★★	★	★★★	7
Ago et al[30]	★★★★	★	★★	7
Hughes et al[31]	★★★★	★	★★★	7
Lv et al[34]	★★★	★	★★★	6
Ferrè et al[32]	★★★	★	★★★	7
Schmaderer et al[35]	★★★	★	★★★	7
Sato et al[36]	★★★★	★	★★★	6
Selim et al[33]	★★★★	★	★★★	7
de Francisco et al[37]	★★★	★	★★★	7
Zhang et al[38]	★★★	★	★★★	7
Ye et al[39]	★★★	★	★★★	7
Li et al[40]	★★★★	★	★★	6
Lu et al[41]	★★★	★	★★★	6
Mizuiri et al[42]	★★★	★	★★★	6
Wu et al[43]	★★★★	★	★★★	7
Ogawa et al[44]	★★★	★	★★★	7
Guan et al[45]	★★★	★	★★★	7

Table 3

The association between serum magnesium and all-cause and cardiovascular mortality in CKD and ESRD patients.

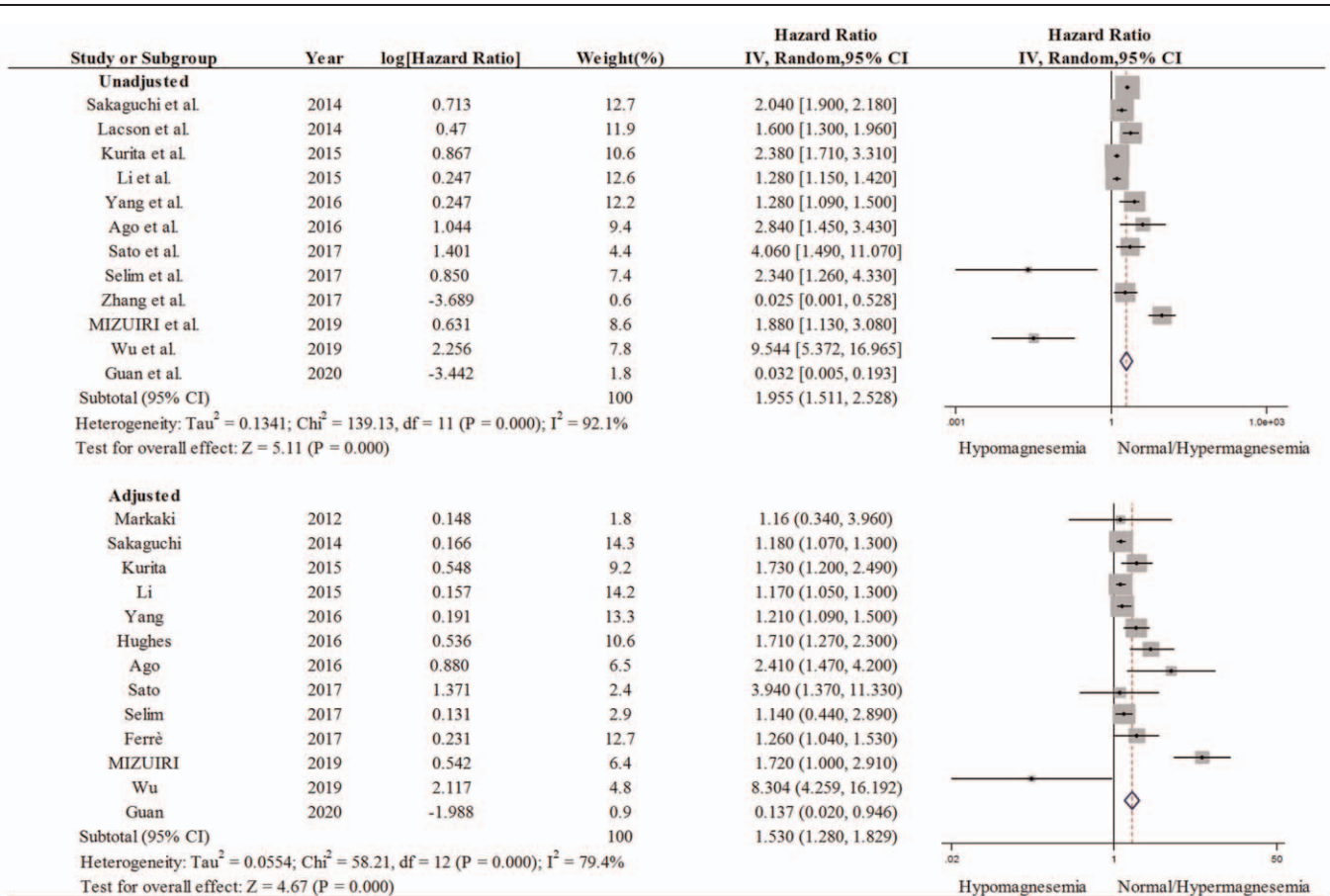| Study	Year	All-cause mortality		Cardiovascular mortality	
		Unadjusted OR or HR (95% CI)	Adjusted OR or HR (95% CI)	Unadjusted OR or HR (95% CI)	Adjusted OR or HR (95% CI)
Ishimura et al[18]	2007	0.261 (0.143, 0.477)[†,§]	0.485 (0.241, 0.975)[†,§]	NR	0.983 (0.313, 3.086)[†,§]
Markaki et al[19]	2012	NR	1.16 (0.34, 3.96)[*,§]	NR	NR
Ortega et al[20]	2013	1.5 (0.15, 14.7)[†,§]	NR	0.4 (0.08, 2.5)[†,§]	NR
Broek et al[21]	2013	NR	0.93 (0.89, 0.98)[†,§]	NR	0.64 (0.39, 1.05)[†,§]
Laecke et al[22]	2013	NR	0.93 (0.89, 0.98)[†,§]	NR	NR
Lacson et al[11]	2014	1.6 (1.3, 1.96)[*,§]	NR	NR	NR
Fein et al[23]	2014	0.142 (0.0354, 0.2486)[†,§]	0.984 (0.9684, 0.9999)[†,§]	NR	NR
Sakaguchi et al[14]	2014	2.04 (1.9, 2.18)[*,‡]	1.18 (1.07, 1.30)[*,‡]	NR	NR
Li et al[24]	2015	1.28 (1.15, 1.42)[*,§]	1.17 (1.05, 1.30)[*,§]	NR	NR
de Roij van Zuijdewijn et al[25]	2015	0.85 (0.77, 0.94)[†,§]	0.88 (0.78, 0.99)[†,§]	0.73 (0.62, 0.85)[†,§]	0.73 (0.62, 0.85)[†,§]
Matias et al[26]	2015	NR	0.87 (0.68, 0.99)[†,§]	NR	0.82 (0.72, 0.95)[†,§]
Garagarza et al[27]	2015	NR	0.489 (0.36, 0.76)[†,§]	NR	NR
Kurita et al[28]	2015	2.38 (1.71, 3.31)[*,§]	1.73 (1.20, 2.49)[*,§]	NR	NR
Yang et al[13]	2016	1.28 (1.09, 1.50)[*,§]	1.21 (1.09, 1.50)[*,§]	NR	NR
Cai et al[29]	2016	0.041 (0.007, 0.223)[†,§]	0.075 (0.01, 0.552)[†,§]	0.007 (0.001, 0.081)[†,§]	0.003 (0, 0.055)[†,§]
Ago et al[30]	2016	2.84 (1.45, 3.43)[*,§]	2.41 (1.47, 4.2)[*,§]	NR	NR
Hughes et al[31]	2016	NR	1.71 (1.27, 2.30)[*,§]	NR	NR
Lv et al[34]	2016	NR	NR	NR	5.617 (1.628, 19.381)[†,§]
Ferrè et al[32]	2017	NR	1.26 (1.04, 1.53)[*,§]	NR	1.14 (0.92, 1.41)[*,§]
Schmaderer et al[35]	2017	0.54 (0.20, 1.46)[†,§]	0.35 (0.13, 0.97)[†,§]	NR	NR
Sato et al[36]	2017	4.06 (1.49, 11.07)[*,§]	3.94 (1.37, 11.33)[*,§]	5.99 (1.26, 28.6)[*,§]	5.57 (1.69, 13.83)[*,§]
Selim et al[33]	2017	2.34 (1.26, 4.33)[*,§]	1.14 (0.44, 2.89)[*,§]	NR	1.68 (0.34, 8.35)[*,§]
de Francisco et al[37]	2017	0.69 (0.54, 0.89)[*,§]	1.28 (0.97, 1.70)[†,§]	NR	NR
Zhang et al[38]	2017	0.025 (0.001, 0.528)[*,‡]	NR	NR	NR
Ye et al[39]	2018	0.85 (0.71, 1.02)[†,§]	0.83 (0.68, 1.01)[†,§]	0.85 (0.67, 1.08)[†,§]	0.82 (0.64, 1.06)[†,§]
Li et al[40]	2019	0.572 (0.338, 0.797)[*,§]	0.226 (0.072, 0.705)[*,§]	0.304 (0.111, 0.829)[*,§]	0.327 (0.119, 0.895)[*,§]
Lu et al[41]	2019	NR	0.017 (0.002, 0.197)[†,§]	NR	0.011 (0.000, 0.269)[†,§]
Mizuiri et al[42]	2019	1.88 (1.13, 3.08)[*,§]	1.72 (1.00, 2.91)[*,§]	NR	NR
Wu et al[43]	2019	9.544 (5.372, 16.965)[*,§]	8.304 (4.259, 16.192)[*,§]	11.211 (4.268, 29.447)[*,§]	9.721 (3.251, 29.066)[*,§]
Ogawa et al[44]	2020	NR	0.32 (0.15, 0.68)[*,§]	NR	NR
Guan et al[45]	2020	0.032 (0.005, 0.193)[*,§]	0.137 (0.020, 0.946)[*,§]	0.017 (0.001, 0.232)[*,§]	0.037 (0.002, 0.636)[*,§]

CI = confidence interval, CKD = chronic kidney disease, ESRD = end stage renal disease, HR = hazard ratio, NR = not reported, OR = odds ratio.
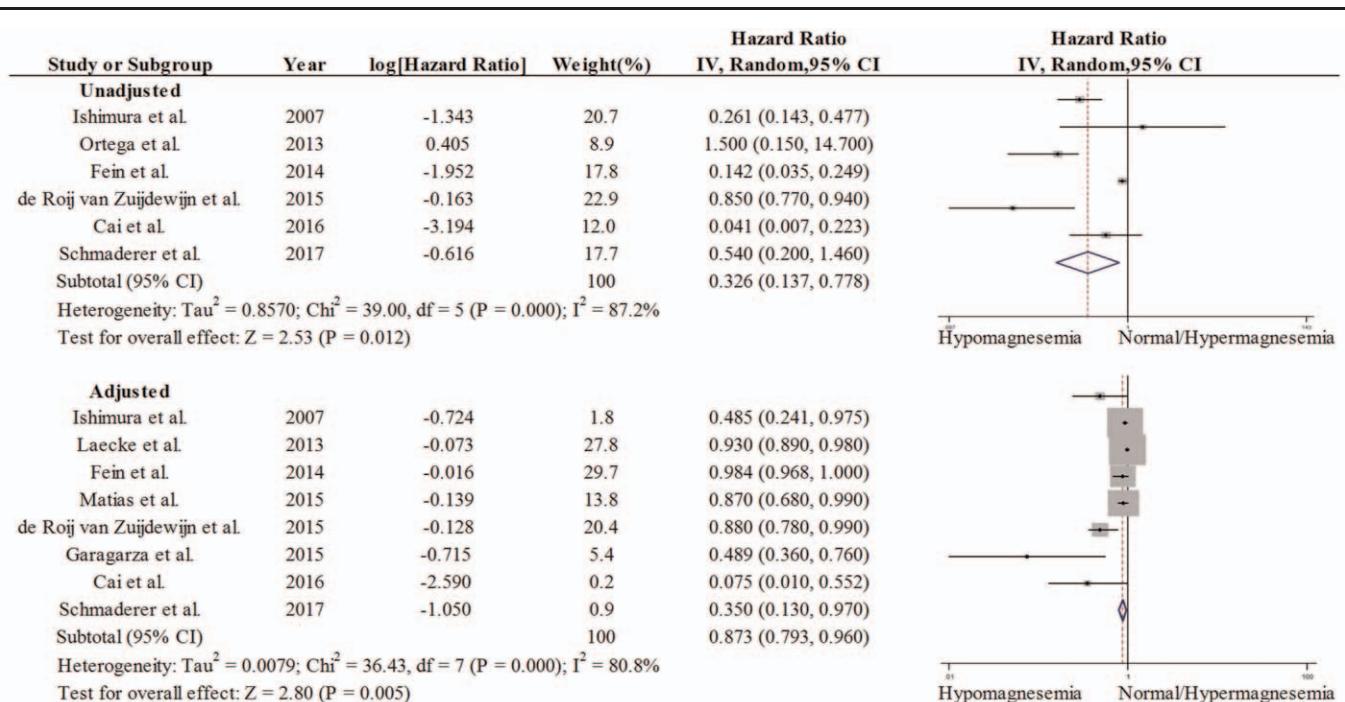
* Reported or calculated by dichotomous variables.

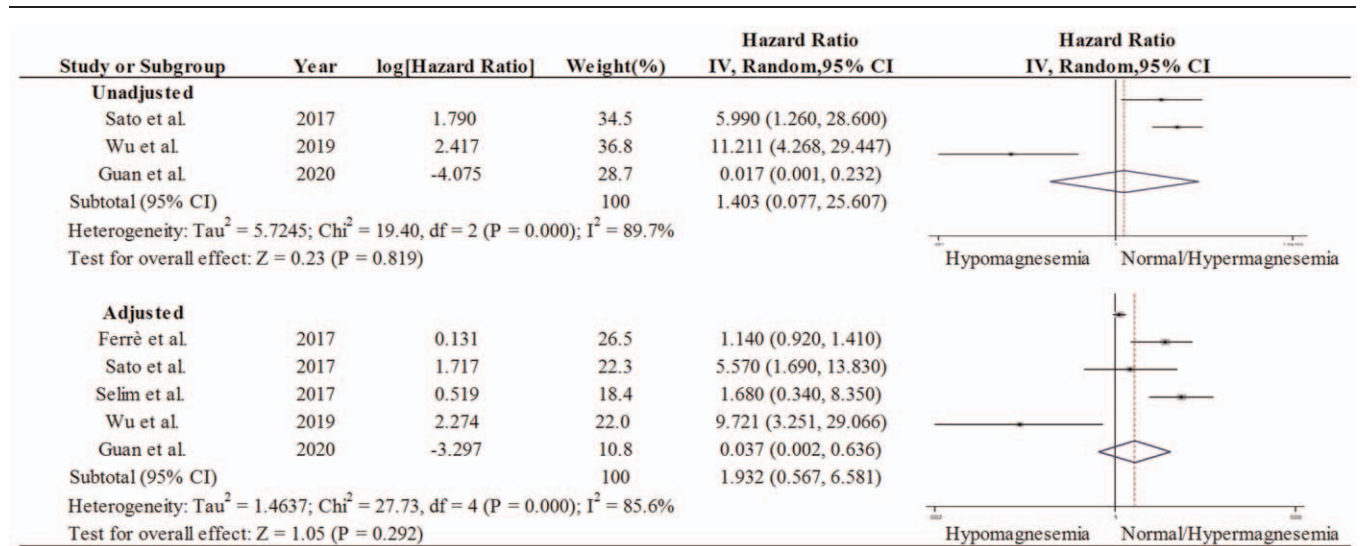† Reported or calculated by continuous variable.

‡ OR was used for risk estimates.

§ HR was used for risk estimates.

Study or Subgroup	Year	log[Hazard Ratio]	Weight(%)	Hazard Ratio IV, Random,95% CI
Unadjusted				
Sakaguchi et al.	2014	0.713	12.7	2.040 [1.900, 2.180]
Lacson et al.	2014	0.47	11.9	1.600 [1.300, 1.960]
Kurita et al.	2015	0.867	10.6	2.380 [1.710, 3.310]
Li et al.	2015	0.247	12.6	1.280 [1.150, 1.420]
Yang et al.	2016	0.247	12.2	1.280 [1.090, 1.500]
Ago et al.	2016	1.044	9.4	2.840 [1.450, 3.430]
Sato et al.	2017	1.401	4.4	4.060 [1.490, 11.070]
Selim et al.	2017	0.850	7.4	2.340 [1.260, 4.330]
Zhang et al.	2017	-3.689	0.6	0.025 [0.001, 0.528]
MIZUIRI et al.	2019	0.631	8.6	1.880 [1.130, 3.080]
Wu et al.	2019	2.256	7.8	9.544 [5.372, 16.965]
Guan et al.	2020	-3.442	1.8	0.032 [0.005, 0.193]
Subtotal (95% CI)			100	1.955 (1.511, 2.528)
Heterogeneity: Tau² = 0.1341; Chi² = 139.13, df = 11 (P = 0.000); I² = 92.1%				
Test for overall effect: Z = 5.11 (P = 0.000)				
Adjusted				
Markaki	2012	0.148	1.8	1.16 (0.340, 3.960)
Sakaguchi	2014	0.166	14.3	1.180 (1.070, 1.300)
Kurita	2015	0.548	9.2	1.730 (1.200, 2.490)
Li	2015	0.157	14.2	1.170 (1.050, 1.300)
Yang	2016	0.191	13.3	1.210 (1.090, 1.500)
Hughes	2016	0.536	10.6	1.710 (1.270, 2.300)
Ago	2016	0.880	6.5	2.410 (1.470, 4.200)
Sato	2017	1.371	2.4	3.940 (1.370, 11.330)
Selim	2017	0.131	2.9	1.140 (0.440, 2.890)
Ferrè	2017	0.231	12.7	1.260 (1.040, 1.530)
MIZUIRI	2019	0.542	6.4	1.720 (1.000, 2.910)
Wu	2019	2.117	4.8	8.304 (4.259, 16.192)
Guan	2020	-1.988	0.9	0.137 (0.020, 0.946)
Subtotal (95% CI)			100	1.530 (1.280, 1.829)
Heterogeneity: Tau² = 0.0554; Chi² = 58.21, df = 12 (P = 0.000); I² = 79.4%				
Test for overall effect: Z = 4.67 (P = 0.000)				

Figure 2. The association between hypomagnesemia and all-cause mortality for dichotomous variables (hypomagnesemia vs normal magnesium or hypermagnesemia group). 95% CI = 95% confidence interval.

Study or Subgroup	Year	log[Hazard Ratio]	Weight(%)	Hazard Ratio IV, Random,95% CI
Unadjusted				
Ishimura et al.	2007	-1.343	20.7	0.261 (0.143, 0.477)
Ortega et al.	2013	0.405	8.9	1.500 (0.150, 14.700)
Fein et al.	2014	-1.952	17.8	0.142 (0.035, 0.249)
de Roij van Zuijdewijn et al.	2015	-0.163	22.9	0.850 (0.770, 0.940)
Cai et al.	2016	-3.194	12.0	0.041 (0.007, 0.223)
Schmaderer et al.	2017	-0.616	17.7	0.540 (0.200, 1.460)
Subtotal (95% CI)			100	0.326 (0.137, 0.778)
Heterogeneity: Tau² = 0.8570; Chi² = 39.00, df = 5 (P = 0.000); I² = 87.2%				
Test for overall effect: Z = 2.53 (P = 0.012)				
Adjusted				
Ishimura et al.	2007	-0.724	1.8	0.485 (0.241, 0.975)
Laecke et al.	2013	-0.073	27.8	0.930 (0.890, 0.980)
Fein et al.	2014	-0.016	29.7	0.984 (0.968, 1.000)
Matias et al.	2015	-0.139	13.8	0.870 (0.680, 0.990)
de Roij van Zuijdewijn et al.	2015	-0.128	20.4	0.880 (0.780, 0.990)
Garagarza et al.	2015	-0.715	5.4	0.489 (0.360, 0.760)
Cai et al.	2016	-2.590	0.2	0.075 (0.010, 0.552)
Schmaderer et al.	2017	-1.050	0.9	0.350 (0.130, 0.970)
Subtotal (95% CI)			100	0.873 (0.793, 0.960)
Heterogeneity: Tau² = 0.0079; Chi² = 36.43, df = 7 (P = 0.000); I² = 80.8%				
Test for overall effect: Z = 2.80 (P = 0.005)				

Figure 3. The association between hypermagnesemia and all-cause mortality for continuous variables (hypermagnesemia vs normal magnesium or hypomagnesemia group). 95% CI = 95% confidence interval.

Figure 4. Subgroup analysis of the association between serum magnesium and all-cause mortality. A. Adjusted HRs in hemodialysis patients (dichotomous variables) (hypomagnesemia vs normal magnesium or hypermagnesemia group). B. Adjusted HRs in hemodialysis patients (continuous variables) (hypomagnesemia vs normal magnesium or hypermagnesemia group). 95% CI = 95% confidence interval, HR = hazard ratio.

between adjusted serum magnesium and cardiovascular disease mortality (HR based on dichotomous variables). The results showed that there was no negative correlation between hypomagnesemia and cardiovascular mortality (HR 1.932; 95% CI 0.567-6.581, $P = .292$, Fig. 5).

The 3 studies listed in Table 3 reported that unadjusted HR (HR is calculated on a continuous variable basis, per unit increase), and there was negative association between hypomagnesemia and mortality from cardiovascular disease (HR 0.156; 95% CI 0.015-1.657, $P = .123$, Fig. 6). However, 6 studies reported the relationship between adjusted serum magnesium and cardiovascular mortality (HR is calculated on a continuous variable basis, per unit increase), and the results showed a significant correlation between hypomagnesemia and a decrease

in mortality from cardiovascular disease (HR 0.598; 95% CI 0.094-1.102, $P = .02$, Fig. 6).

3.4. Sensitivity analysis

After removing each including article one by one, the sensitivity analysis was conducted. However, the result demonstrated that there was no significant change in the results of the combined effect, which implied that the result of meta-analysis was stable.
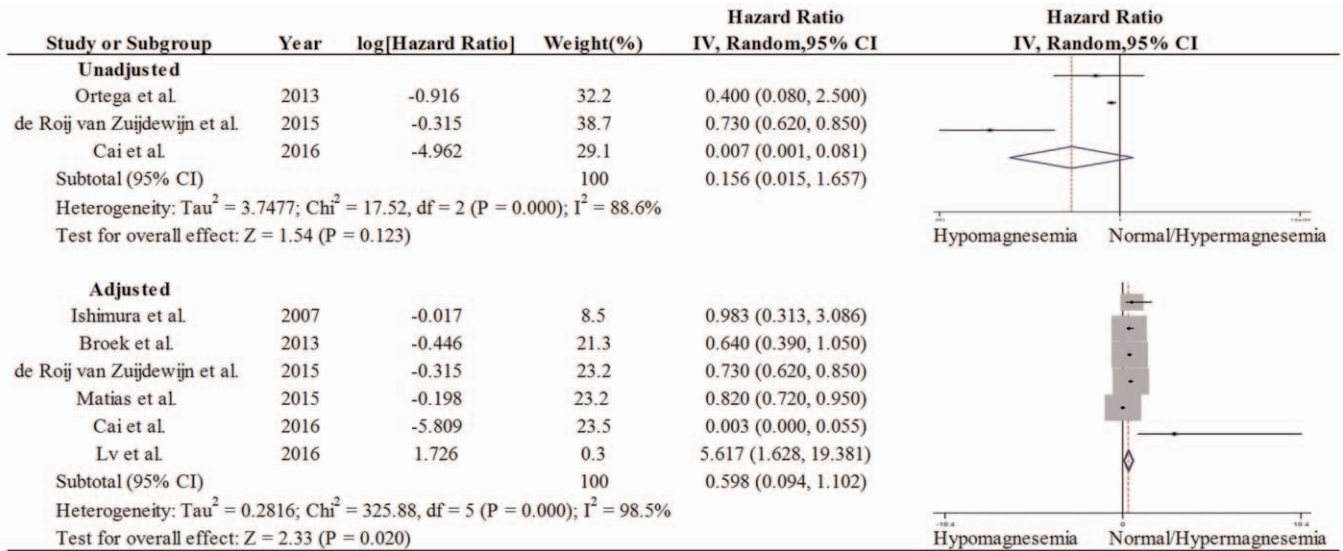
3.5. Publication bias

Begg test and Egger test were used to assess publication bias (Fig. 7). Symmetry of the funnel plots implies that there is no

Table 4

Subgroup analysis of serum magnesium and all-cause mortality with a random effect model.

Group	Number of studies	Pooled HR	95% CI	P (heterogeneity)	I^2 (%)
All studies	13	1.530	1.280-1.829	.000	79.4
Location					
Asia	8	1.836	1.326-2.543	.000	86.6
Non-Asia	5	1.274	1.108-1.464	.226	29.4
Age					
≥60	9	1.794	1.402-2.297	.000	84.9
<60	4	1.198	0.973-1.476	.166	40.9
Length of follow-up (yrs)					
≥5	5	1.193	1.070-1.330	.257	24.7
<5	8	2.093	1.430-3.065	.000	85.8
Participants predisposition					
Dialysis	11	1.578	1.270-1.960	.000	81.4
CKD	2	1.436	1.068-1.932	.091	65.0
Methodological quality					
NOS score ≥7	8	1.576	1.206-2.060	.000	85.3
NOS score <7	5	1.549	1.113-2.154	.037	60.9
Study design					
Prospective	6	1.724	0.928-3.204	.000	82.4
Retrospective	7	1.272	1.132-1.431	.031	56.8

CI = confidence interval, CKD = chronic kidney disease, HD = hemodialysis, HR = hazard ratio, NOS = Newcastle–Ottawa Scale, PD = peritoneal dialysis.

Study or Subgroup	Year	log[Hazard Ratio]	Weight(%)	Hazard Ratio IV, Random,95% CI	Hazard Ratio IV, Random,95% CI
Unadjusted					
Ortega et al.	2013	-0.916	32.2	0.400 (0.080, 2.500)	
de Roij van Zuijdewijn et al.	2015	-0.315	38.7	0.730 (0.620, 0.850)	
Cai et al.	2016	-4.962	29.1	0.007 (0.001, 0.081)	
Subtotal (95% CI)			100	0.156 (0.015, 1.657)	
Heterogeneity: Tau^2 = 3.7477; Chi^2 = 17.52, df = 2 (P = 0.000); I^2 = 88.6%					
Test for overall effect: Z = 1.54 (P = 0.123)					
					Hypomagnesemia Normal/Hypermagnesemia
Adjusted					
Ishimura et al.	2007	-0.017	8.5	0.983 (0.313, 3.086)	
Broek et al.	2013	-0.446	21.3	0.640 (0.390, 1.050)	
de Roij van Zuijdewijn et al.	2015	-0.315	23.2	0.730 (0.620, 0.850)	
Matias et al.	2015	-0.198	23.2	0.820 (0.720, 0.950)	
Cai et al.	2016	-5.809	23.5	0.003 (0.000, 0.055)	
Lv et al.	2016	1.726	0.3	5.617 (1.628, 19.381)	
Subtotal (95% CI)			100	0.598 (0.094, 1.102)	
Heterogeneity: Tau^2 = 0.2816; Chi^2 = 325.88, df = 5 (P = 0.000); I^2 = 98.5%					
Test for overall effect: Z = 2.33 (P = 0.020)					Hypomagnesemia Normal/Hypermagnesemia

Figure 5. The association between serum magnesium and cardiovascular mortality for dichotomous variables (hypomagnesemia vs normal magnesium or hypermagnesemia group). 95% CI = 95% confidence interval.
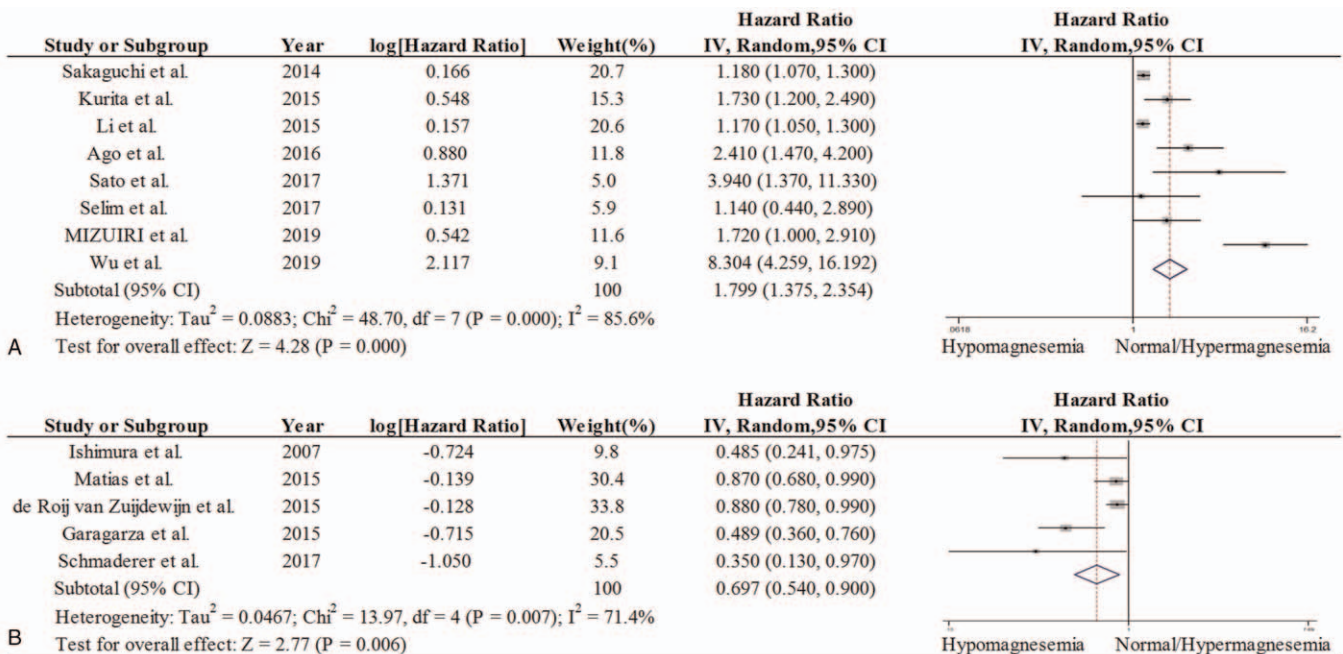
obvious publication bias in Begg test (P=.625), and the results of Egger test suggest no evidence of publication bias either (P=.16).

4. Discussion

In this study, we performed a systematic review and meta-analysis of all relevant literature, identified 31 original articles, and reported the relationship between serum magnesium levels and all-cause and cardiovascular mortality in patients with chronic kidney disease and dialysis. The results of the study showed that serum magnesium levels were negatively associated with increased all-cause mortality in patients with CKD and ESRD.

The dynamic balance of serum magnesium is controlled by a variety of factors including intestinal uptake, renal excretion, and bone exchange.[10] Thus, reduced dietary intake of magnesium, poor intestinal absorption or renal dysfunction can lead to hypomagnesemia.[46] The prevalence of hypomagnesemia in the

Study or Subgroup	Year	log[Hazard Ratio]	Weight(%)	Hazard Ratio IV, Random,95% CI	Hazard Ratio IV, Random,95% CI
Sakaguchi et al.	2014	0.166	20.7	1.180 (1.070, 1.300)	
Kurita et al.	2015	0.548	15.3	1.730 (1.200, 2.490)	
Li et al.	2015	0.157	20.6	1.170 (1.050, 1.300)	
Ago et al.	2016	0.880	11.8	2.410 (1.470, 4.200)	
Sato et al.	2017	1.371	5.0	3.940 (1.370, 11.330)	
Selim et al.	2017	0.131	5.9	1.140 (0.440, 2.890)	
MIZUIRI et al.	2019	0.542	11.6	1.720 (1.000, 2.910)	
Wu et al.	2019	2.117	9.1	8.304 (4.259, 16.192)	
Subtotal (95% CI)			100	1.799 (1.375, 2.354)	
Heterogeneity: Tau^2 = 0.0883; Chi^2 = 48.70, df = 7 (P = 0.000); I^2 = 85.6%					
A Test for overall effect: Z = 4.28 (P = 0.000)					Hypomagnesemia Normal/Hypermagnesemia

Study or Subgroup	Year	log[Hazard Ratio]	Weight(%)	Hazard Ratio IV, Random,95% CI	Hazard Ratio IV, Random,95% CI
Ishimura et al.	2007	-0.724	9.8	0.485 (0.241, 0.975)	
Matias et al.	2015	-0.139	30.4	0.870 (0.680, 0.990)	
de Roij van Zuijdewijn et al.	2015	-0.128	33.8	0.880 (0.780, 0.990)	
Garagarza et al.	2015	-0.715	20.5	0.489 (0.360, 0.760)	
Schmaderer et al.	2017	-1.050	5.5	0.350 (0.130, 0.970)	
Subtotal (95% CI)			100	0.697 (0.540, 0.900)	
Heterogeneity: Tau^2 = 0.0467; Chi^2 = 13.97, df = 4 (P = 0.007); I^2 = 71.4%					
B Test for overall effect: Z = 2.77 (P = 0.006)					Hypomagnesemia Normal/Hypermagnesemia

Figure 6. The association between hypermagnesemia and cardiovascular mortality for continuous variables (hypermagnesemia vs normal magnesium or hypomagnesemia group). 95% CI = 95% confidence interval.
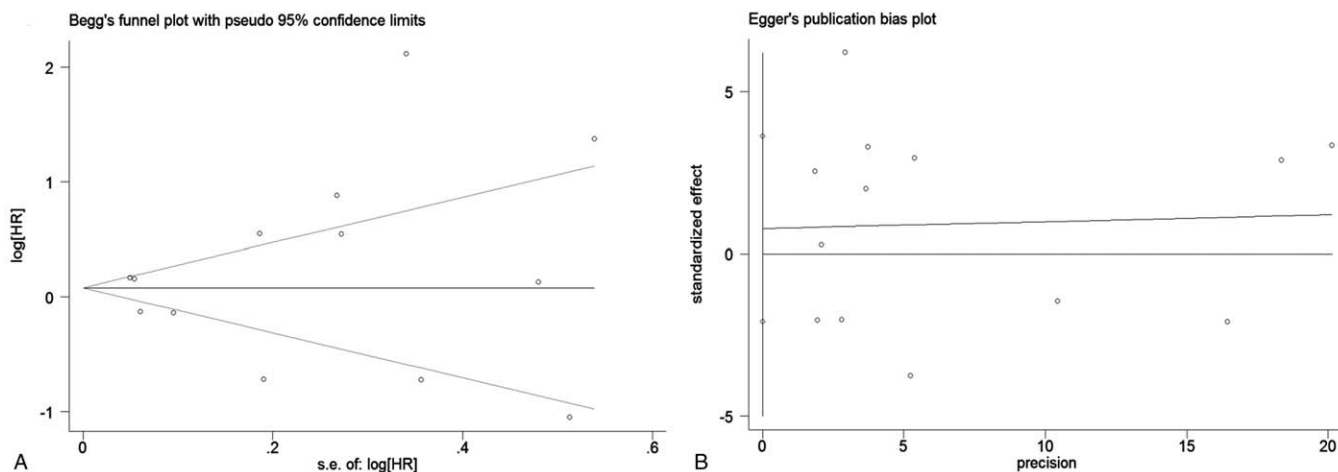
Figure 7. Funnel plot of the associations between magnesium and all-cause mortality. A. The funnel plot with pseudo 95% confidence intervals (CIs). B. Egger publication bias plot. HR = hazard ratio.

general population is about 15%, and the incidence in intensive care units can be 4 times higher.[47] Clinical evidence shows that magnesium has a protective effect on cardiovascular disease in the general population.[48] In a study of atherosclerosis risk in communities, hypomagnesemia was found to be significantly associated with an increased risk of cardiovascular disease.[49] In another prospective study, urine and plasma magnesium excretion tests were performed on 7664 adults without cardiovascular disease. The results of this study showed that reduced excretion of magnesium from urine is accompanied by an increased risk of ischemic heart disease. Conversely, the risk of ischemic heart disease can be reduced if the intake of magnesium ions in the diet is increased.[50] Similar results were observed in a cohort study, which showed that oral treatment with medications containing magnesium ions was inversely associated with mortality from coronary heart disease, heart failure, and overall cardiovascular disease in women.[51] There are numerous studies and ample evidence that serum magnesium levels play an important physiological role in the maintenance of normal cardiovascular function.[52] The results of several studies have shown that magnesium ions inhibit vascular calcification by acting directly on the vessel wall and indirectly throughout the body.[53,54] However, the role of serum magnesium ion levels in chronic kidney disease and its impact on cardiovascular morbidity and mortality has not yet been conclusively established. In patients with advanced chronic kidney disease, serum magnesium levels and magnesium dynamic balance change from time to time, which may lead to significantly increased morbidity and mortality from cardiovascular disease in patients with chronic kidney disease.[55] Zaher et al[56] conducted a study to assessed the relationship between serum magnesium levels and vascular sclerosis in children who received regular HD. The results showed that serum magnesium levels were significantly lower in children with conventional HD compared to the control group. In addition, as serum magnesium levels decline, the risk of vascular calcification increases. An epidemiological study of patients with CKD showed a significant association between serum magnesium and both all-cause and cardiovascular mortality. Ishimura et al[18] reported for the first time the relationship between serum magnesium levels and mortality in

maintenance HD patients and found that hypomagnesemia was an important factor in the increased mortality in maintenance HD patients. Cai et al[29] conducted a study which also found that hypomagnesemia was significantly associated with increased all-cause mortality and cardiovascular mortality in peritoneal dialysis patients. Similarly, Kanbay et al[57] conducted a study that showed a significant association between serum magnesium levels below 2.05 mg/dL and increased cardiovascular mortality in patients with CKD on maintenance dialysis. However, Ortega et al[20] conducted a study to assess the association between serum magnesium levels and all-cause and cardiovascular mortality in patients with advanced CKD not receiving dialysis. The results did not find serum magnesium levels to be an independent predictor of all-cause and cardiovascular mortality in patients with CKD. But the occurrence of these opposite results may be due to the influence of limited patient numbers and follow-up periods. Salford conducted a study on the kidney, recruiting more than 1000 patients with CKD to assess the association between serum magnesium levels and all-cause mortality. The results showed that hypomagnesemia was significantly associated with an increase in all-cause mortality.[32] However, whether hypomagnesemia is associated with an increased risk of all-cause and cardiovascular mortality in patients with CKD has not been widely reported or uniformly conclusive, and only the results of 1 study suggest that hypomagnesemia is an independent predictor of increased mortality in patients with CKD.[32] Therefore, more research is needed to confirm this result.

The exact biological mechanisms underlying the dynamic balance of magnesium ions and the risk of all-cause and cardiovascular mortality in humans are now unclear. Association between low serum magnesium levels and inflammation and immunodeficiency may contribute to increased mortality in patients with CKD.[58] The association between serum calcium, phosphate, and mortality in patients with CKD has been confirmed by numerous studies.[59] However, the association between serum magnesium levels and mortality in patients with CKD is unclear. A recent study has shown that calcium magnesium citrate supplementation can inhibit the formation of troponin granules, inhibit parathyroid hormone, and give

magnesium and base load to patients in stages 3 and 5 of CKD.[60] However, Sakaguchi et al[14] conducted a large cohort study and showed that serum phosphorus levels increased the risk of cardiovascular mortality only in the low and normal magnesium groups, but not in the high magnesium group. They therefore concluded that serum magnesium levels significantly reduced the risk of cardiovascular death associated with hyperphosphate in maintenance dialysis patients, which increased the association between magnesium and phosphate and the risk of cardiovascular death. The Kidney disease: improving CKD minerals and bone abnormalities (CKD-MBD) global prognosis (KDIGO) guidelines provide recommendations for the diagnosis and treatment of calcium and phosphate rather than magnesium.[61] Evidence that magnesium is associated with mortality in patients with end-stage renal disease and maintenance dialysis suggests that clinicians should carefully monitor serum magnesium levels in HD patients. Maintaining normal or mildly elevated serum magnesium levels may be beneficial in improving cardiovascular prognosis in HD patients. However, whether CKD and dialysis patients benefit from magnesium supplementation is unclear and further prospective studies are needed to test this hypothesis.

We conducted this meta-analysis incorporating data from 31 cohort studies including 205,436 subjects from different countries and regions. There are several limitations to the study. One of the major limitations was that each subject had only 1 measurement of serum magnesium levels at admission. We were unable to calculate specific values for serum magnesium associated with all-cause and cardiovascular mortality because of the wide variation in patient levels of serum magnesium and limited data. In the included studies, the types of magnesium were different (continuous variables, dichotomous variables and high magnesium level, low magnesium level, and normal magnesium level), which may also lead to heterogeneity. Secondly, 4 conference summaries are included for analysis, which did not have complete available data, so we could not fully assess the quality of the study. Third, the study design includes prospective and retrospective studies, which may cause heterogeneity, and our subgroup analysis does show that based on the stratification of the study design, there is an essential difference in the risk of all-cause death. Due to the difference of multivariate adjustment factors, there are confounding factors in the adjusted HR of each study report, which may also lead to bias. Finally, our conclusions on the association between serum magnesium levels and all-cause and cardiovascular mortality should receive adequate attention in patients with CKD. However, further clinical randomized controlled trials are still needed to validate the effect of serum magnesium levels and magnesium-supplemented medications on prognosis of patients with CKD and ESRD.

Author contributions

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Investigation: Hongyan Liu, Rui Wang.
Methodology: Hongyan Liu, Rui Wang.
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Supervision: Hongyan Liu, Rui Wang.
Visualization: Hongyan Liu, Rui Wang.
Writing – original draft: Hongyan Liu, Rui Wang.
Writing – review & editing: Hongyan Liu, Rui Wang.

References

[1] de Baaij JH, Hoenderop JG, Bindels RJ. Magnesium in man: implications for health and disease. Physiol Rev 2015;95:1–46.

[2] Volpe SL. Magnesium in disease prevention and overall health. Adv Nutr 2013;4:378–83.

[3] Hruby A, Meigs JB, O'Donnell CJ, Jacques PF, McKeown NM. Higher magnesium intake reduces risk of impaired glucose and insulin metabolism and progression from prediabetes to diabetes in middle-aged Americans. Diabetes Care 2014;37:419–27.

[4] Shechter M. Magnesium and cardiovascular system. Magnes Res 2010;23:60–72.

[5] Massy ZA, Drueke TB. Magnesium and outcomes in patients with chronic kidney disease: focus on vascular calcification, atherosclerosis and survival. Clin Kidney J 2012;5:52–61.

[6] Qu X, Jin F, Hao Y, et al. Magnesium and the risk of cardiovascular events: a meta-analysis of prospective cohort studies. PLoS One 2013;8: e57720.

[7] Del Gobbo LC, Imamura F, Wu JH, de Oliveira Otto MC, Chiuve SE, Mozaffarian D. Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 2013;98:160–73.

[8] Song Y, Manson JE, Cook NR, Albert CM, Buring JE, Liu S. Dietary magnesium intake and risk of cardiovascular disease among women. Am J Cardiol 2005;96:1135–41.

[9] Tonelli M, Wiebe N, Culleton B, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol 2006;17:2034–47.

[10] Blaine J, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. Clin J Am Soc Nephrol 2015;10:1257–72.

[11] Lacson EJr, Wang W, Ma L, Passlick-Deetjen J. Serum magnesium and mortality in hemodialysis patients in the United States: a cohort study. Am J Kidney Dis 2015;66:1056–66.

[12] Li L, Streja E, Rhee CM, et al. Hypomagnesemia and mortality in incident hemodialysis patients. Am J Kidney Dis 2015;66:1047–55.

[13] Yang X, Soohoo M, Streja E, et al. Serum magnesium levels and hospitalization and mortality in incident peritoneal dialysis patients: a cohort study. Am J Kidney Dis 2016;68:619–27.

[14] Sakaguchi Y, Fujii N, Shoji T, Hayashi T, Rakugi H, Isaka Y. Hypomagnesemia is a significant predictor of cardiovascular and non-cardiovascular mortality in patients undergoing hemodialysis. Kidney Int 2014;85:174–81.

[15] Khatami MR, Mirchi E, Khazaeipour Z, Abdollahi A, Jahanmardi A. Association between serum magnesium and risk factors of cardiovascular disease in hemodialysis patients. Iran J Kidney Dis 2013;7:47–52.

[16] Hartling L, Milne A, Hamm MP, et al. Testing the Newcastle Ottawa Scale showed low reliability between individual reviewers. J Clin Epidemiol 2013;66:982–93.

[17] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[18] Ishimura E, Okuno S, Yamakawa T, Inaba M, Nishizawa Y. Serum magnesium concentration is a significant predictor of mortality in maintenance hemodialysis patients. Magnes Res 2007;20:237–44.

[19] Markaki A, Kyriazis J, Stylianou K, et al. The role of serum magnesium and calcium on the association between adiponectin levels and all-cause mortality in end-stage renal disease patients. PLoS One 2012;7:e52350.

[20] Ortega O, Rodriguez I, Cobo G, et al. Lack of influence of serum magnesium levels on overall mortality and cardiovascular outcomes in patients with advanced chronic kidney disease. ISRN Nephrol 2013;2013:191786.

[21] Broek JSVD, Hoekstra T, Drechsler C, Brandenburg MG, Vervloet MG. Association of magnesium level with reduced cardiovascular mortality in incident dialysis patients. Nephrol Dial Transpl 2013;28:i11.

[22] Van Laecke S, Nagler EV, Verbeke F, Van Biesen W, Vanholder R. Hypomagnesemia and the risk of death and GFR decline in chronic kidney disease. Am J Med 2013;126:825–31.

[23] Fein P, Weiss S, Ramos F, Singh P, Chattopadhyay J, Avram MM. Serum magnesium concentration is a significant predictor of mortality in peritoneal dialysis patients. Adv Perit Dial 2014;30:90–3.

[24] Li L, Liang W, Ye T, et al. The association between nutritional markers and biochemical parameters and residual renal function in peritoneal dialysis patients. PLoS One 2016;11:e0156423.

[25] de Roij van Zuijdewijn CLM, Grooteman MPC, Bots ML, et al. Serum magnesium and sudden death in European hemodialysis patients. PLoS One 2015;10:e0143104.

[26] João Matias P, Azevedo A, Laranjinha I, et al. Lower serum magnesium is associated with cardiovascular risk factors and mortality in haemodialysis patients. Blood Purif 2015;38:244–52.

[27] Garagarza C, Valente AT, Oliveira TA, Caetano C, Ribeiro S. Magnesium and body composition are associated with mortality in prevalent hemodialysis patients: myth or reality? Clin Nutr 2015; 34:183.

[28] Kurita N, Akizawa T, Fukagawa M, Onishi Y, Kurokawa K, Fukuhara S. Contribution of dysregulated serum magnesium to mortality in hemodialysis patients with secondary hyperparathyroidism: a 3-year cohort study. Clin Kidney J 2015;8:744–52.

[29] Cai K, Luo Q, Dai Z, et al. Hypomagnesemia is associated with increased mortality among peritoneal dialysis patients. PLoS One 2016;11: e0152488.

[30] Ago R, Shindo T, Banshodani M, et al. Hypomagnesemia as a predictor of mortality in hemodialysis patients and the role of proton pump inhibitors: a cross-sectional, 1-year, retrospective cohort study. Hemodial Int 2016;20:580–8.

[31] Hughes J, Chiu D, Kalra P, Green D. Extremes of serum magnesium are associated with an independent increase in all-cause mortality in a chronic kidney disease population. Nephrol Dial Transplant 2016; 31:425.

[32] Ferrè S, Li X, Adams-Huet B, et al. Association of serum magnesium with all-cause mortality in patients with and without chronic kidney disease in the Dallas Heart Study. Nephrol Dial Transplant 2018;33:1389–96.

[33] Selim GN, Spasovski G, Tozija L, et al. Hypomagnesemia and cause-specific mortality in hemodialysis patients: 5-year follow-up analysis. Int J Artif Org 2017;13:542–9.

[34] Lv Y, Mi E, Zhou X. Hypomagnesia is associated with risk factors of cardiovascular death in maintenance hemodialysis patients. Chin J Integr Tradit West Nephrol 2016;17:537–9.

[35] Schmaderer C, Braunisch MC, Suttmann Y, et al. Reduced mortality in maintenance haemodialysis patients on high versus low dialysate magnesium: a pilot study. J Nutr 2017;9:926–36.

[36] Sato H, Takeuchi Y, Matsuda K, et al. Evaluation of the predictive value of the serum calcium-magnesium ratio for all-cause and cardiovascular mortality in incident dialysis patients. J Cardiorenal Med 2017;1:50–60.

[37] de Francisco ALM, Varas J, Ramos R, et al. Proton pump inhibitor usage and the risk of mortality in hemodialysis patients. J Kidney Int Rep 2017;3:374–84.

[38] Zhang J, Yang Z, Ma M. Study on the correlation between blood magnesium and death in severe hemodialysis patients. J China Modern Doctor 2017;55:8–11.

[39] Ye H, Cao P, Zhang X, et al. Serum magnesium and cardiovascular mortality in peritoneal dialysis patients: a 5-year prospective cohort study. Br J Nutr 2018;120:415–23.

[40] Luo-hua L, Jing L, Jin-han Z, Hong-ying J, Yi-hua B, Yun-ping D. Association between low serum magnesium level and mortality in maintenance hemodialysis dialysis patients. J Modern Prev Med 2019;46:4216–20.

[41] Lu C, Wang Y, Wang D, et al. Hypomagnesemia and short-term mortality in elderly maintenance hemodialysis patients. J Kidney Dis (Basel) 2019;6:109–18.

[42] Mizuiri S, Nishizawa Y, Yamashita K, et al. Relationship of serum magnesium level with body composition and survival in hemodialysis patients. J Hemodial Int 2019;24:99–107.

[43] Wu L, Cai K, Luo Q, Wang L, Hong Y. Baseline serum magnesium level and its variability in maintenance hemodialysis patients: associations with mortality. J Kidney Blood Press Res 2019;44:222–32.

[44] Ogawa C, Tsuchiya K, Maeda K. High serum magnesium levels are associated with favorable prognoses in diabetic hemodialysis patients, retrospective observational study. PLoS One 2020;15:e0238763.

[45] Guan J, Gong T, Gong S. Association of serum magnesium with cardiovascular mortality and all-cause mortality in peritoneal dialysis patients. Chin J Nephrol 2020;36:688–95.

[46] Agus ZS. Mechanisms and causes of hypomagnesemia. Curr Opin Nephrol Hypertens 2016;25:301.

[47] Fairley J, Glassford NJ, Zhang L, Bellomo R. Magnesium status and magnesium therapy in critically ill patients: a systematic review. J Crit Care 2015;30:1349–58.

[48] Del Gobbo LC, Imamura F, Wu JHY, de Oliveira Otto MC, Chiuve SE, Mozaffarian D. Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 2013;98:160–73.

[49] Lutsey PL, Alonso A, Michos ED, et al. Serum magnesium, phosphorus, and calcium are associated with risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study. Am J Clin Nutr 2014;100:756–64.

[50] Joosten MM, Gansevoort RT, Mukamal KJ, et al. Urinary and plasma magnesium and risk of ischemic heart disease. Am J Clin Nutr 2013;97:1299–306.

[51] Zhang W, Iso H, Ohira T, Date C, Tamakoshi A. JACC Study GroupAssociations of magnesium intake with mortality from cardiovascular disease. Atherosclerosis 2012;221:587–95.

[52] Kolte D, Vijayaraghavan K, Khera S, et al. Role of magnesium in cardiovascular diseases. Cardiol Rev 2014;22:182–92.

[53] Neven E, De Schutter TM, Dams G, et al. A magnesium based phosphate binder reduces vascular calcification without affecting bone in chronic renal failure rats. PLoS One 2014;9:e107067.

[54] Herencia C, Rodríguez-Ortiz ME, Muñoz-Castañeda JR, et al. Angiotensin II prevents calcification in vascular smooth muscle cells by enhancing magnesium influx. Eur J Clin Investig 2015;45:1129–44.

[55] Massy ZA, Drüeke TB. Magnesium and cardiovascular complications of chronic kidney disease. Nat Rev Nephrol 2015;11:432.

[56] Zaher MM, Abdel-Salam M, Abdel-Salam R, Sabour R, Morsy AA, Gamal D. Serum magnesium level and vascular stiffness in children with chronic kidney disease on regular hemodialysis. Saudi J Kidney Dis Transpl 2016;27:233–40.

[57] Kanbay M, Yilmaz MI, Apetrii M, et al. Relationship between serum magnesium levels and cardiovascular events in chronic kidney disease patients. Am J Nephrol 2012;36:228–37.

[58] Sugimoto J, Romani AM, Valentin-Torres AM, et al. Magnesium decreases inflammatory cytokine production: a novel innate immunomodulatory mechanism. J Immunol 2012;188:6338–46.

[59] Da J, Xie X, Wolf M, et al. Serum phosphorus and progression of CKD and mortality: a meta-analysis of cohort studies. Am J Kidney Dis 2015;66:258–65.

[60] Quiñones H, Hamdi T, Sakhaee K, Pasch A, Moe OW, Pak CYC. Control of metabolic predisposition to cardiovascular complications of chronic kidney disease by effervescent calcium magnesium citrate: a feasibility study. J Nephrol 2018;32:93–100.

[61] Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work GroupKDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl 2009;76:1–130.