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ORIGINAL ARTICLE

Vitamin D status and mortality risk among patients on dialysis: a systematic review and meta-analysis of observational studies

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ABSTRACT

Background. Vitamin D deficiency is highly prevalent in patients on dialysis. Although vitamin D deficiency is closely associated with cardiovascular disease (CVD) and high mortality in the general population, the relationship between serum 25-hydroxyvitamin D [25(OH)D] and all-cause and cardiovascular mortality in dialysis patients is uncertain. We aim to explore the relationship between serum 25(OH)D levels and all-cause and cardiovascular mortality in dialysis patients.

Methods. This is a systematic review and meta-analysis of clinical studies among patients receiving maintenance dialysis. We did a systematic literature search in PubMed and Embase to identify studies reporting the relationship between serum 25(OH)D levels and all-cause and cardiovascular mortality in patients on dialysis. The search was last updated on 10 February 2017.

Results. The study included 18 moderate to high-quality cohort studies with an overall sample of 14 154 patients on dialysis. The relative risk of all-cause mortality per 10 ng/mL increase in serum 25(OH)D level was 0.78 [95% confidence interval (CI) 0.71–0.86], although there was marked heterogeneity ($I^2 = 96\%$, $P < 0.01$) that was partly explained by differences in CVD prevalence, baseline parathyroid hormone level and dialysis duration among included studies. The relative risk of cardiovascular mortality per 10 ng/mL increase in serum 25(OH)D level was 0.71 (95% CI 0.63–0.79), with substantial heterogeneity ($I^2 = 74\%$, $P = 0.004$) that was largely explained by differences in study type and serum 25(OH)D measurement method.

Conclusions. In the present study, increased serum 25(OH)D level was significantly associated with lower all-cause mortality and lower cardiovascular mortality in dialysis patients.

Keywords: dialysis, end-stage renal disease, meta-analysis, systematic review, vitamin D

INTRODUCTION

The serum level of 25-hydroxyvitamin D [25(OH)D] is widely used to determine vitamin D status [1]. Recent guidelines defined vitamin D sufficiency as a serum 25(OH)D level >30 ng/mL (75 nmol/L) for those not on dialysis [2]. In patients on dialysis, there is no established cutoff for vitamin D deficiency. Factors including inadequate sun exposure, malnutrition, reduced capacity to produce 25(OH)D in the skin and loss of vitamin D–binding protein via dialysate all contribute to a lower vitamin D level [3, 4]. If a serum 25(OH)D level of 30 ng/mL is applied as a cutoff, the estimated prevalence of vitamin D deficiency among dialysis patients ranges from 50% to 100% [5], much higher than the prevalence in the general population [6].

In the general population, studies among adults, elders, children and patients with diabetes mellitus (DM) showed that higher vitamin D levels were associated with a lower mortality rate [7–10]. A meta-analysis of prospective cohort studies designed to evaluate the association between vitamin D level and mortality risk in the general population showed a nonlinear decrease in mortality risk as circulating 25(OH)D increased [11]. In the dialysis population, vitamin D deficiency was found to be associated with increased risks of vascular calcification [12], stroke [13], left ventricular hypertrophy [14] and cardiovascular events [13], each of which was in turn associated with increased mortality. However, observational data from patients on dialysis inconsistently demonstrate an association between low 25(OH)D levels and increased mortality [13, 15–28]. A previous meta-analysis showed that higher 25(OH)D levels were associated with improved survival in CKD patients [29]. However, the number of dialysis patients included in this meta-analysis was quite limited [29].

Therefore, we performed a meta-analysis of observational studies reporting serum 25(OH)D levels and all-cause and

cardiovascular mortality in patients on dialysis to determine whether or not a relationship was present.

MATERIALS AND METHODS

This meta-analysis was conducted and reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [30].

Search strategy

We performed a systematic literature search in PubMed/MEDLINE and Embase to identify relevant studies. We used the keywords [vitamin D OR 25(OH)D OR cholecalciferol OR 25(OH)D] AND (mortality OR death OR fatal OR survival) AND (dialysis OR kidney OR renal OR uremia). Reference lists of selected articles were scanned manually to identify any other relevant articles. Studies were considered without language restrictions. When information needed for analysis was not available, we wrote to the corresponding author for raw data. The search was updated on 10 February 2017.

Selection criteria

Reports fulfilling the following inclusion criteria were included in the meta-analysis: (i) patient population comprised adults on dialysis, (ii) cohort studies or clinical trials that reported associations between serum vitamin D status and mortality rate and (iii) risk ratio (RR)/hazard ratio (HR)/odds ratio (OR) associated with serum vitamin D level or each category of serum vitamin D level was reported together with a corresponding measure of uncertainty [95% confidence interval (CI) or standard errors or P-value for the significance of the estimate] or the author provided us with raw data necessary to estimate the above-mentioned information. When results of a single study were published in more than one article, we used the most recent one with the largest sample of individuals. The literature was searched and eligible studies identified by two investigators (Y.H.Z. and H.C.P.) independently. Disagreements were resolved by discussion between the two investigators.

Primary outcomes

The outcomes were all-cause mortality and cardiovascular mortality.

Data extraction and quality assessment

Data extraction was performed with the use of a dataset designed before we began the search for studies. The dataset contained information regarding study type, length of follow-up, sample size, participants' characteristics and estimates of the association of 25(OH)D levels with mortality risk. For studies that reported results for continuous 25(OH)D, we extracted risk estimates (RRs/HRs/ORs and corresponding 95% CIs) for all-cause mortality and cardiovascular mortality per unit increase in baseline vitamin D level with the most comprehensive control for potential confounding. For studies that reported RRs for categorized baseline serum 25(OH)D levels, we recorded risk estimates and the corresponding categorical ranges of serum 25(OH)D level. Finally, we recorded covariates that were adjusted for in each study.

The Newcastle–Ottawa scale (range 0–9) was used to assess the quality of included studies of an individual. A table containing the ratings for each included study is shown in Supplementary data, Table S1. In the current study we considered a study with a score $\geq$7 as a high-quality study, a study with a score of 4–7 as a moderate-quality study and a study with a score $\leq$4 as a low-quality study.

Statistical methods

Estimates of risk and model fitting. First, we unified the RRs of the 18 included studies to a 10 ng/mL (25 nmol/L) increase in serum 25(OH)D level (Supplementary data, Table S2). For each included study that used categorized serum 25(OH)D, we transformed RRs and corresponding 95% CIs into RRs for mortality per unit increase in serum 25(OH)D level according to the method provided by Greenland and Longnecker [31]. Several studies reporting RR for categorized serum 25(OH)D did not give the number of deaths for each category of vitamin D level, so we extracted the data from published Kaplan–Meier curves using the data extraction software 'GetData' [http://getdata-graph-digitizer.com (25 January 2018, date last accessed)]. In the study by Pečovnik-Balon *et al.* [25], the article provided only Kaplan–Meier curves instead of any form of RR for mortality. We therefore extracted data from the Kaplan–Meier curves and used the method from Tierney *et al.* [32] to calculate the HR. For studies presenting their results as ORs, we transformed them to RRs using the method of Zhang and Yu [33]. HRs and RRs were used interchangeably in the meta-analysis.

Second, we conducted a generic variance meta-analysis using a random effects model. The association between vitamin D level and all-cause and cardiovascular mortality was computed as a summary RR with 95% CI. The summary RR was considered statistically significant if the 95% CI did not include 1.0 or if the P-value was $<$0.05.

R version 3.4.0 (R Project for Statistical Computing, Vienna, Austria) was used for the transformation of RR by Greenland and Longnecker [31] in this study. Review Manager 5.3 was used for the generic variance meta-analysis.

Heterogeneity and sensitivity analysis. Heterogeneity was evaluated using the I^2 parameter. To investigate the source of marked heterogeneity observed in our meta-analysis, we performed subgroup analysis to evaluate the effect of some potential factors, including study type, sample size, study quality, the measurement method for serum 25(OH)D, dialysis modality and geographic region. Then we further explored through meta-regression the effect of differences in adjustment for covariates influencing survival [including vitamin D supplementation and baseline parathyroid hormone (PTH)]; differences in data transformation method by which RR was derived; different measures of effect provided by single studies (HR or OR); percentage of patients on vitamin D supplementation; baseline levels of PTH, 25(OH)D, calcium and phosphate; prevalence of cardiovascular disease (CVD) and DM; length of follow-up;

mean age of the study population; publication year and dialysis duration. The influential analysis was conducted to test if a particular study contributed appreciably to the observed heterogeneity. We also examined the stability of results in sensitivity analyses by excluding studies with extreme RRs from the meta-analysis. Publication bias was tested by funnel plot.

Review Manager 5.3 was used for the subgroup analysis. Stata 12.0 (StataCorp, College Station, TX, USA) was used for meta-regression analysis, sensitivity analyses and testing for publication bias.

RESULTS

Study selection

Our systemic literature search was updated until 10 February 2017, and identified 3100 abstracts: 1368 abstracts in PubMed and 1732 abstracts in Embase. There were no articles of interest in languages other than English. Of the 3100 references, we excluded 3057 by the screening of titles and abstracts, which left 43 abstracts to source for full text. After further exclusion of conference abstracts and studies with duplicate study populations, 17 articles were left for further evaluation. Through discussion with the expert in this field, one additional study was also included for evaluation. We identified no additional references from a search of reference lists of the 18 full-text articles. We reviewed the full texts of the 18 studies and e-mailed the authors for raw data of studies that did not report estimates for the endpoint of interest. All 18 independent cohort studies were ultimately included in our meta-analysis, which either reported data for 25(OH)D levels and mortality risks in the article or the individual raw data provided to us by the author of the article. Detailed steps of the literature search and study selection are shown in Figure 1.

Study characteristics

Included studies were published between 2009 and 2017 [13, 16–28, 34–38] and involved 14 154 patients on dialysis. Table 1 shows the characteristics of included studies.

Most studies were prospective cohort studies, except for the studies by Krause *et al.* [19] and Walker *et al.* [37], which were both retrospective cohort studies, and the study by Wolf *et al.* [28], which was a nested case–control study from a prospective cohort. All studies examined the association between vitamin D and all-cause mortality, with five studies also examining the association between vitamin D and cardiovascular mortality [19, 23, 24, 27, 36]. Among all included studies, 3 were conducted in Asia, 5 in the USA and 10 in Europe. All studies were community based. Barreto *et al.* [27] included both patients with predialysis CKD and patients on hemodialysis; only the data for patients on dialysis were included in this meta-analysis. Ogawa *et al.* [20] excluded patients with a history of CVD. The mean age of participants in included studies ranged from 55 to 71 years. The mean follow-up ranged from 0.25 to 9 years. The number of deaths ranged from 18 to 3010. Considering the assay method for serum 25(OH)D, nine studies [13, 16, 18, 19, 23, 24, 27, 36, 37] used a chemiluminescence assay, three used radioimmunoassays [20, 28, 38], three used an enzyme immunoassay or enzyme-linked immunosorbent assay [22, 25, 26] and one study used chromatography–tandem mass spectrometry [34].

Based on the Newcastle–Ottawa scale, we assessed the quality of included studies. A total of 10 of 18 studies were of high quality, 7 were of moderate quality and 1 was assessed as low quality (Supplementary data, Table S1).

The estimates for the association between 25(OH)D level and all-cause mortality from each included study are shown in Table 2. The estimates for the association of 25(OH)D level and cardiovascular mortality from the included studies are presented in Table 3.

Association of serum vitamin D level with all-cause mortality. A forest plot of RRs per 10 ng/mL (25 nmol/L) increase in 25(OH)D level is shown in Figure 2. Summary RR estimates indicate a 22% decrease in mortality risk associated with each 10 ng/mL increase of serum level of 25(OH)D. Significant between-study heterogeneity was found ($I^2 = 96\%$, $P < 0.001$). Meta-regression suggested that the prevalence of CVD ($P = 0.039$), baseline level of PTH ($P = 0.172$) and dialysis duration ($P = 0.326$) contributed to some of the observed heterogeneity. After adjusting for the prevalence of CVD, baseline level of PTH and prevalence of DM, the I^2 value dropped to 57%. By adjusting for baseline level of PTH and dialysis duration, the I^2 value dropped to 0% in the remaining six studies in which data were available for both factors. None of the other factors contributed appreciably to the observed heterogeneity (Supplementary data, File S1).

Subgroup analysis showed that studies with a lower prevalence of CVD presented greater ($P = 0.08$) RR estimates [RR 0.87 (95% CI 0.76–1.00)] than studies with a higher prevalence [RR 0.72 (95% CI 0.61–0.84)]; studies with a higher PTH level showed an insignificantly ($P = 0.42$) lower RR [RR 0.73 (95% CI 0.56–0.94)] than those with a lower PTH level [RR 0.81 (95% CI 0.73–0.91)] (Supplementary data, Table S3). In subgroup analysis based on different methods for generating RR, the group of studies with additional data derived from Kaplan–Meier curves showed the most significant heterogeneity ($I^2 = 98\%$). After exclusion of this group, the I^2 value dropped to 70% without a significant change in overall results [RR 0.81 (95% CI 0.76–0.85)].

In the sensitivity analysis, systematically omitting one study at a time did not change the overall estimate of effect. The I^2 value dropped to 83% after omitting the study by Schiller *et al.* [16]. After further exclusion of the study by Ogawa *et al.* [20], the I^2 value was further reduced to 67%, with a materially unchanged result [RR 0.80 (95% CI 0.75–0.85)] (Supplementary data, File S3). No significant publication bias can be seen on the funnel plot (Supplementary data, Figure S1).

Effects of serum vitamin D level on cardiovascular mortality rate. A forest plot of RRs per 10 ng/mL (25 nmol/L) increase in 25(OH)D level is shown in Figure 3. The summary RR estimate indicates a 29% decrease in cardiovascular mortality associated with each 10 ng/mL increase of serum 25(OH)D level. Significant between-study heterogeneity was found ($I^2 = 74\%$, $P = 0.004$). Meta-regression suggested that measurement method

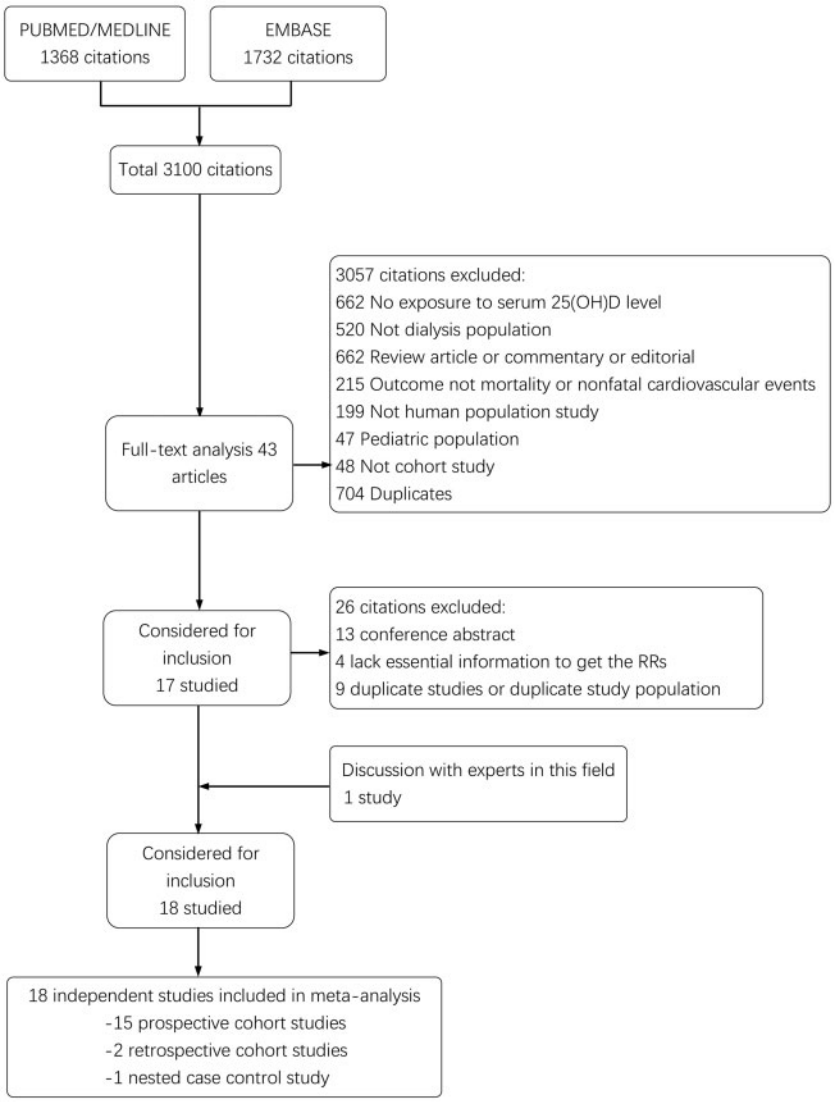

FIGURE 1: Flow chart of selection of included studies.

for serum 25(OH)D (P = 0.114) and study type (P = 0.427) contributed to some of the observed heterogeneity. Heterogeneity was not apparent after adjusting for the above factors ($I^2 = 0\%$) (Supplementary data, File S2). In the sensitivity analysis, systematically omitting one study at a time did not materially change the overall estimate of effect. Excluding the study by Krause *et al.* [19] decreased the I^2 value to 52%, with the summary RR altered to 0.58 (95% CI 0.41–0.82) (Supplementary data, File S3). No significant publication bias can be seen on the funnel plot (Supplementary data, Figure S2).

DISCUSSION

This meta-analysis showed that an increased serum level of 25(OH)D was associated with reduced all-cause mortality and cardiovascular mortality in 14 154 dialysis patients drawn from 18 cohort studies. Although the studies were generally of moderate to high quality, marked heterogeneity related to study differences in CVD prevalence, baseline PTH level, dialysis duration, serum 25(OH)D measurement method and study type was observed. This finding could be of clinical significance in that the serum level of 25(OH)D could be a predictive factor for all-cause mortality and cardiovascular mortality, as well as a marker to identify high-risk patients.

Our result is in accordance with current Kidney Disease: Improving Global Outcomes guidelines suggesting the correction of vitamin D deficiency to the target level of at least 30–40 ng/mL in patients with CKD [40]. Improving the serum level of 25(OH)D by supplementation of natural vitamin D in patients on dialysis may be an effective way to improve survival and has been reported to be beneficial for various health outcomes in previous studies [41–43].

Vitamin D deficiency has been reported to be associated with increased mortality among dialysis patients in many studies [13, 16–19, 21–24, 27, 28, 34, 36, 37]. However, the results have not been consistent. The predictive effect of vitamin D on mortality is potentially influenced by many factors. Since patients with vitamin D deficiency are usually sicker, with more

Table 1. Characteristics of included studies

Source	Study type (cohort)	No. of patients	Mean age (years)	Male (%)	DM (%)	CVD (%)	Accrual period	F/U (years)	Died	Assay methods	Dialysis modality	Country
Wolf *et al.* [28]	Nested-case control	984	63 ± 15	53	43	NA	2004–05	0.25	244	Dia RIA	HD	USA
Wang *et al.* [26]	Prospective	230	55 ± 12	51	30	19.1	NA	3	70	IDS ELISA	PD	Hong Kong
Barreto *et al.* [27]	Prospective	46	67 ± 12	61	42	NA	2006–07	1.7	18	Dia CLIA	33% HD	France
Gracia-Iguacel *et al.* [23]	Prospective	115	60 ± 16	62	28	37	2007	1.2	20	Dia CLIA	82% HD 18%PD	Spain
Pečovnik-Balon *et al.* [25]	Prospective	102	61 ± 13	57	NA	NA	2005–07	2	27	IDS EIA	HD	Slovenia
Drechsler *et al.* [13]	Prospective	1108	66 ± 8	54	100	30	1998–2002	4	545	Dia CLIA	HD	Germany
Drechsler *et al.* (NECOSAD) [24]	Prospective	762	59 ± 15	61	20	32	NA	3	213	Dia CLIA	64% HD 36% PD	The Netherlands
Anand *et al.* [22]	Prospective	256	62 ± 14	55	58.6	37	2005–07	3.8	NA	Direct Enzyme Immunoassay	91% HD 9% PD	USA
Ogawa *et al.* [20]	Prospective	100	60.6 ± 11.9	64	31	0	2006–11	4.6	24	Dia RIA	HD	Japan
Krause *et al.* [191]	Retrospective	6518	71 (19 ± 98)	58.6	34.9	NA	1997–2006	9	3010	Competitive protein-binding assay[a] Nichols advantage assay[b]	HD	Germany
Jean *et al.* [18]	Prospective	648	67.1 ± 13	60	32	NA	2005–09	3.5	169	DiaSorin LIAISON[c]	HD	France
Fiedler *et al.* [17]	Prospective	81	64 (24 ± 91)	58	33.3	NA	2003–06	3	34	NA	HD	Germany
Schiller *et al.* [16]	Prospective	570	55 ± 13	54.6	16.1	64.6	2010–11	1.16	68	Dia CLIA	HD	Romania
Chonchol *et al.* [34]	Prospective	1340	57 ± 14	45	43.8	78.8	1995–2000	3	582	Chromatography-tandem mass spectrometry	HD	USA
Scialla *et al.* [35]	Prospective	511	57.9 ± 14.8	55	57	56	1995–98	3.4	361	IDS	HD	USA
Chen *et al.* [36]	Prospective	110	55.2 ± 1.4	58.2	13.6	NA	2011	3.5	25	Electrochemiluminescence immunoassay	HD	China
Walker *et al.* [37]	Retrospective	128	66.8 ± 11.7	96.9	60.9	50	2003–12	2.73	40	CLIA	HD	USA
Bozkurt *et al.* [38]	Prospective	545	58 ± 14	54	22	21	2005–06	1.83	76	RIA	HD	Turkey

CLIA, chemiluminescence assay; Dia, DiaSorin; EIA, enzyme immunoassay; F/U, follow-up; HD, hemodialysis; IDS, immunodiagnostic systems; NA, not applicable; PD, peritoneal dialysis; RIA, radioimmunoassay.

[a]Competitive protein-binding assay. This method was developed in-house. The laboratory values were adjusted in Krause's study to be comparable with the Nichols Advantage 25(OH)D assay.

[b]Nichols Advantage assay. A two-site chemiluminescence assay that relies on binding of vitamin D to a vitamin D–binding protein purified from human sources. There have been some problems with the Nichols Advantage 25(OH)D method. It failed to consistently show the expected increase in vitamin D [39].

[c]A two-site chemiluminescence assay that uses an antibody against 25(OH)D.

Table 2. Estimates for the association of 25(OH)D and all-cause mortality reported in the included studies

Source	Number of deaths	25(OH)D (ng/mL)	At risk	25(OH)D category	RR (95% CI)		Adjustments
					Categorical analysis	Continuous analysis	
Wolf *et al.* [28]	244	21	187	<10	1.6 (1.0–2.4)		Age, sex, race, cause of kidney failure, standardized mortality rates, BP, vascular access, albumin, creatinine, PTH, Ca, P, Hb, history of CAD, stroke, malignancy, CHF
			594	10–30	1.3 (0.9–1.8)		
			203	>30	1.0 (ref)		
Wang *et al.* [26]	70	18.3	116	≤18.3	P = 0.9, higher mortality for ≤18.3	1.06 (0.59–1.89) per log 25(OH)D in nmol/L	NA
			114	>18.3			
Barreto *et al.* [27]	18	21	46	–	–	0.91 (0.85–0.97) per 1 ng/mL	Age, PTH
Gracia-Iguacel *et al.* [23]	20	15.15	115	–	–	0.90 (0.81–0.98) per 1 ng/mL	Age, sex, DM, CVD
Pečovnik-Balon *et al.* [25]	27	23.3	49	≤20	P = 0.033, higher mortality for ≤20		NA
			53	>20			
Drechsler *et al.* [13]	22.9/100 p-y	8.0	177	≤10	1.65 (1.14–2.38)	1.36 (1.13–1.64) per log 25(OH)D in nmol/L	Age, sex, atorvastatin, season, CAD, CHF, SBP, smoking, dialysis duration, BMI, ultrafiltration volume, LDLC, HDLC, CRP, HbA_1C, beta-blockers, ACEIs, diuretics, PTH, Ca, P
	17.1/100 p-y	14.0	607	10 to ≤20	1.20 (0.86–1.68)		
	15.1/100 p-y	24.5	210	20 to ≤30	1.16 (0.80–1.70)		
	13/100 p-y	37.7	114	>30	1.00 (ref)		
Drechsler *et al.* (NECOSAD) [24]	213	8	193	≤10	1.25 (0.71–2.18)	NA	Age, sex, dialysis modality, ethnicity, primary kidney disease, DM, CVD, BMI, SBP, smoking, cholesterol, vitamin supplements, ALB, Hb, SCr, seasonal variation of vitamin D
		18	469	10 to ≤30	0.84 (0.52–1.38)		
		40	100	>30	1.00 (ref)		
Anand *et al.* [22]	NA	12.9	85	<10.6	1.75 (1.03–2.97)	0.63 (0.42–0.97) per 10 ng/mL 25(OH)D	Age, gender, race, BMI, DM, dialysis modality, facility.
			86	10.6 to ≤15.5	1.55 (0.86–2.80)		
			85	>15.5	1.00 (ref)		
Ogawa *et al.* [20]	24	21.87	55	< 20	1.04 (0.97–1.11)	NA	Age, dialysis vintage, BMI, hemoglobin, serum levels of albumin, total cholesterol, CRP, Ca, P, PTH, use of alfacalcidol
			45	≥20	1.00 (ref)		
Krause *et al.* [19]	3010	19.96	2686	<12.5	1.74 (1.63–1.85)	NA	Age, gender, DM, year of incidence
			1162	12.5 to <20	1.29 (1.15–1.42)		
			1097	20 to <30	1.12 (0.99–1.25)		
			1573	≥30	1.00 (ref)		
Jean *et al.* [18]	169	27	324	<18	1.00 (ref)	NA	Age, gender, diabetes, Ca, P, peripheral vascular and cardiac disease and dialysis vintage
			324	≥18	0.73 (0.50–0.96)		
Fiedler *et al.* [17]	34	14.13	38	≤12	2.76 (1.33–5.73)	NA	Age
			43	>12	1.00 (ref)		
Schiller *et al.* [16]	68	22.8	162	>30	1.00 (ref)	NA	Age, gender, dialysis duration, PVD, ischemic cardiomyopathy, stroke, diabetes and vitamin D supplementations
			290	10–30	0.837 (0.425–1.651)		
			118	<10	1.619 (0.787–3.327)		
Chonchol *et al.* [34]	582	19.1	335	<14	1.00 (ref)	NA	Age, gender, race, DM, CVD, dialysis duration, smoking status, urea Kt/V, dialysis membrane flux assignments, central catheter use, Ca, P, iPTH, 1, 25(OH)D, serum FGF_2, ALB, hs-CRP, IL-6, TNF-a, and IF-g. Vitamin D analog administration
			335	14–19	0.57 (0.45–0.73)		
			335	19–26	0.50 (0.38–0.65)		
			335	>26	0.46 (0.34–0.62)		
Scialla *et al.* [35]	361	13	511	NA	NA	1 (0.98–1.02) per 1 ng/mL decrease	Age, sex, race, education, smoking, BMI, baseline ICED, DM, CVD, ALB, Hb
Chen *et al.* [36]	25	20.64	110	NA	NA	0.98 (0.97–1.00) per 1 nmol/L	Age, sex, ALB, cardiac valve calcification, aortic artery calcification
Walker *et al.* [37]	28	NA	71	<20	2.342 (1.1–3.61)		Age, HD by central catheter, CAD, ALB, HbA_1C
	12		57	>20	1.00		
Bozkurt *et al.* [38]	76	39	545	NA		0.99 (0.98–1.00) per 1 ng/mL increase	NA

Serum 25(OH)D levels are presented in ng/mL [conversion factor for 25(OH)D in ng/mL to nmol/L, ×2.5).

25(OH)D, 25-hydroxyvitamin D; 1,25(OH)D, 1,25 dihydroxyvitamin D; ACEI, angiotensin-converting enzyme inhibitor; ALB, albumin; BMI, body mass index; BP, blood pressure; Ca, calcium; CAD, coronary artery disease; CHF, congestive heart failure; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein, Hb, hemoglobin; HbA_1C, glycosylated hemoglobin; ICED, Index of Coexistent Disease; IL, interleukin; iPTH, intact parathyroid hormone; LDL-C, low-density lipoprotein cholesterol; P, phosphorus; PVD, peripheral vascular disease; SBP, systolic blood pressure; SCr, serum creatinine; TNF, tumor necrosis factor; p-y, patient-years.

Table 3. Estimates for the association of 25(OH)D and cardiovascular mortality reported in the included studies

Source	No. of CVD deaths	25(OH)D (ng/mL)	At risk	25(OH)D category	RR (95% CI)		Adjustments
					Categorical analysis	Continuous analysis	
Barreto *et al.* [27]	11	21	46	–	–	0.93(0.88–0.99) per 1 ng/mL	Age, PTH
Gracia-Iguacel *et al.* [23]	5	15.15	115	–	–	0.99(0.89–1.11) per 1 ng/mL	Age, sex, DM, CVD
Drechsler (NECOSAD) *et al.* [24]	118	18	193	≤10	2.11 (0.90–4.93)		Age, gender, dialysis modality, ethnicity, primary kidney disease, DM, CVD, BMI, SBP, smoking, cholesterol, use of vitamin supplements, ALB, Hb, SCr, seasonal variation of vitamin D
			469	10–≤30	1.24 (0.58–2.66)		
			100	>30	1.00 (ref)		
Krause *et al.* [19]	1148	23.3	2686	<12.5	1.57 (1.30–1.88)		Age, gender, DM, year of incidence
			1162	12.5–<20	1.26 (1.01–1.58)		
			1097	20–<30	1.07 (0.85–1.35)		
			1573	≥30	1.00 (ref)		
Chen *et al.* [36]	NA	20.64	110			0.962 (0.941–0.984) per 1 nmol/L	Age, ALB, cardiac valve calcification, aortic artery calcification

Serum 25(OH)D levels are presented in ng/mL [conversion factor for 25(OH)D in ng/mL to nmol/L, ×2.5).
25(OH)D, 25-hydroxyvitamin D; 1,25(OH)D, 1,25 dihydroxyvitamin D; ALB, albumin; BMI, body mass index; BP, blood pressure; Ca, calcium; CAD, coronary artery disease; CHF, congestive heart failure; CRP, C-reactive protein; Hb, hemoglobin; SBP, systolic blood pressure; SCr, serum creatinine; TNF, tumor necrosis factor.

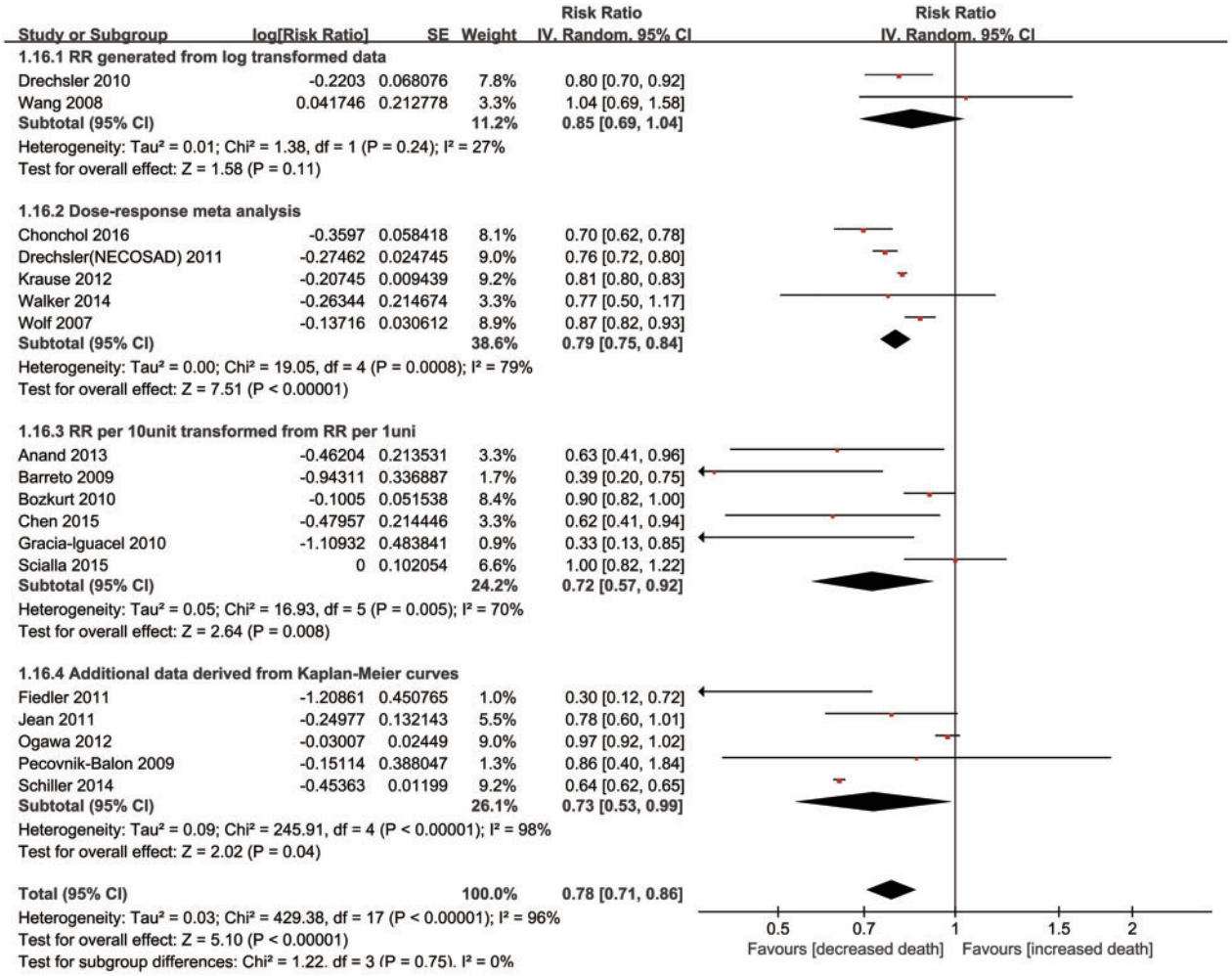

FIGURE 2: Forest plot and summary RR of the association between serum 25(OH)D level and all-cause mortality risk in subgroup analysis based on data transformation method used for generating RR in each study. Results are based on a total number of 14 154 individuals. Vertical marks represent RRs; horizontal bars represent 95% CIs. A statistically significant effect was assumed when the 95% CI did not include 1 (vertical line).

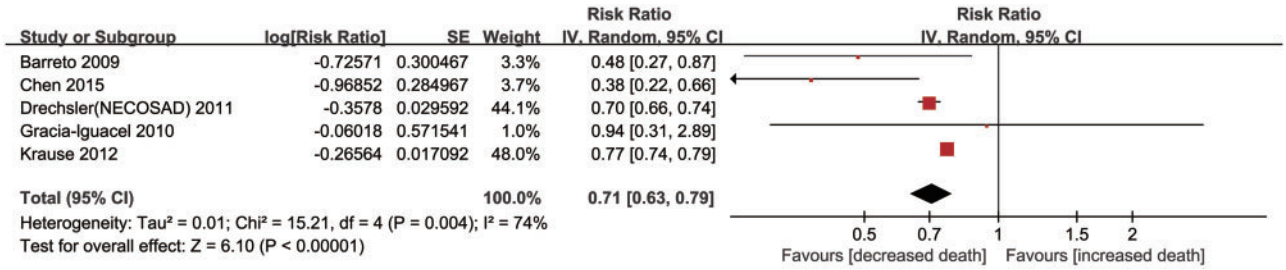

FIGURE 3: Forest plot and summary RR of the association between serum 25(OH)D level and cardiovascular mortality risk. Results are based on a total number of 7551 individuals. Vertical marks represent RRs; horizontal bars represent 95% CIs. A statistically significant effect was assumed when the 95% CI did not include 1 (vertical line).

comorbidities and less time spent outdoors [44], the differences in baseline comorbidity status and different adjustments for confounders among studies may potentially contribute to the inconsistency of results. In one study, Ogawa *et al.* [20] reported no significant association between 25(OH)D levels and all-cause mortality but excluded patients with a known history of a severe cardiac disease, cerebral vascular disease and peripheral artery disease, which are all risk factors for a higher mortality. Schiller *et al.* [16] found that very low 25(OH)D was associated with higher mortality; however, the statistical strength of the association disappeared after adjusting for some common risk factors for mortality. In our subgroup analysis, studies with a higher proportion of patients with established CVD showed a lower RR when compared with studies reporting a lower prevalence of CVD, indicating that the predictive value of vitamin D deficiency for mortality may be more marked in patients with CVD. Vitamin D deficiency in dialysis patients might therefore be a consequence of high-risk conditions instead of a determinant for survival.

Other confounders include serum PTH level and supplementation of active vitamin D, which are both recognized factors associated with mortality. In particular, Wolf *et al.* [24] found that low vitamin D levels were associated with mortality only in patients with high PTH levels. This association was not apparent in patients who received active vitamin D therapy. These findings are consistent with those reported by Pečovnik-Balon *et al.* [25] and Ogawa *et al.* [20]. In our study, subgroup analysis showed a slightly lower RR in studies with higher PTH levels than in those with lower PTH levels. Consequently, lack of adjustment for serum PTH level and vitamin D supplementation in several studies may have also contributed to the inconsistent results.

Vitamin D deficiency has also been identified as a potential risk factor for CVD [45], accounting for approximately half of all deaths in dialysis patients [46]. While it has been demonstrated that 25(OH)D suppresses the renin–angiotensin system, which in turn decreases cardiac myocyte hypertrophy and hypertension, 25(OH)D is also capable of activating the vitamin D receptor (VDR) directly with a 100-fold lower affinity that is compensated for by its 1000-fold higher serum concentration [47]. Another possible mechanism might be related to the immune-regulatory effect of vitamin D, as inflammation plays an important role in the pathogenesis of atherosclerosis [48]. Drechsler *et al.* [24] observed that severe vitamin D deficiency [25(OH)D <10 ng/mL] was associated with increased cardiovascular mortality, while not with noncardiovascular mortality. They reported similar results in the 4D Study, whereby patients with severe vitamin D deficiency presented an increased risk of sudden cardiac death and combined cardiovascular events [13]. Wang *et al.* [26] reported an association between lower serum 25(OH)D level and increased risk of cardiovascular events in patients on peritoneal dialysis, with the relationship being more apparent in the early stage of the cardiac disease. Barreto *et al.* [27] also indicated that low serum 25(OH)D level was associated with mortality independent of vascular calcification and stiffness, suggesting that 25(OH)D may influence survival in the CKD population via additional pathways. However, due to the limited number of studies included, their generally small sample sizes and their frequent lack of adjustment for important confounders, the association between serum vitamin D level with cardiovascular mortality remained of low certainty.

Our meta-analysis has several strengths. First, we included all available studies following a comprehensive systematic review. Additional information was sought and obtained from study authors. Second, our meta-analysis targeted the dialysis population, which has both a high prevalence of vitamin D deficiency and high early mortality risk, thereby providing ideal conditions for studying the association between vitamin D deficiency and mortality risk.

However, our study was also limited by several factors. First, marked heterogeneity was observed among included studies, which was partly related to differences in CVD prevalence, baseline PTH level, dialysis duration, serum 25(OH)D measurement method and study type. The possible effects of differences in data transformation methods used in each study could not be excluded either. Second, potential residual confounding could not be excluded. Most studies provided HRs adjusted for relevant covariates influencing survival rate, but lack of adjustment for vitamin D supplements and baseline PTH level constituted a potential source of residual confounding. However, excluding studies that did not control for these covariates did not change the overall finding. Finally, serum 25(OH)D was tested only once at baseline, but serum 25(OH)D levels are influenced by factors such as variance in dietary intake and seasonal fluctuations.

In conclusion, the current systematic review and meta-analysis of observational studies found that higher serum 25(OH)D level was associated with lower all-cause mortality and lower cardiovascular mortality in dialysis patients. Regular

measurement of serum 25(OH)D may help to identify high-risk patients and provide timely treatment for better prognosis.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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CONFLICT OF INTEREST STATEMENT

None declared.

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