

# Meta-analysis of the association between sclerostin level and adverse clinical outcomes in patients undergoing maintenance haemodialysis

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## Abstract

**Background:** Studies regarding the relationship of sclerostin (Scl) with clinical outcomes in patients undergoing maintenance haemodialysis have yielded controversial findings. This meta-analysis was performed to investigate the predictive role of Scl in this patient population.

**Methods:** Several electronic medical databases (e.g. PubMed, Embase, Web of Science and Cochrane Library) were searched for eligible studies through December 20, 2019. Summary hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated based on Scl level (high or low) using a random or fixed effects model.

**Results:** From among 641 initially screened publications, 16 eligible studies were included in this meta-analysis. A high Scl level was not associated with cardiovascular events [HR=0.8 (95% CI, 0.42–1.35)] or all-cause mortality [HR=0.93 (95% CI, 0.56–1.54)]. There was high heterogeneity, but no evidence of publication bias. Interestingly, a high Scl level was associated with reduced cardiovascular events [HR=0.44 (95% CI, 0.29–0.69)] in the subgroup by shorter follow-up period or all-cause mortality [pooled HR=0.58 (95% CI, 0.36–0.91)] by shorter dialysis vintage.

**Conclusion:** This meta-analysis indicated that a high Scl level did not predict total clinical outcomes in patients undergoing maintenance haemodialysis despite survival benefits in the subgroups. The predictive role of Scl in these patients should be further evaluated in large prospective studies.

**Keywords:** cardiovascular events, haemodialysis, mortality, outcome, sclerostin

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## Introduction

Patients with chronic kidney disease (CKD) exhibit higher risks of cardiovascular (CV) morbidity and mortality;<sup>1</sup> these risks are increased 10–20-fold for patients undergoing maintenance haemodialysis (MHD).<sup>2,3</sup> Thus, risk stratification and assessment are critical for improvement of patient prognosis in this population. However, because of the lack of reliable biomarkers, timely identification of high-risk patients remains challenging.<sup>4,5</sup> CV morbidity and mortality are greatly affected by many classical

and non-classical risk factors;<sup>1</sup> of these, chronic kidney disease–mineral and bone disorder (CKD-MBD) has been recognised as a clinically significant pathophysiologic disorder that predicts adverse outcomes in patients undergoing MHD.<sup>6,7</sup> Although considerable progress has been made in recent decades, the exact mechanisms underlying the correlation of CKD-MBD with adverse outcomes are not fully understood. Sclerostin (Scl) is a glycoprotein, which is encoded by the *SOST* gene.<sup>8</sup> Scl is produced and secreted by osteocytes; it exerts

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various metabolic effects on bone and other tissues through inhibition of canonical WNT signalling.<sup>9</sup> Thus, Scl is emerging as an essential modulator of bone formation and bone mass;<sup>10</sup> it is presumed to participate in the pathogenesis and progression of CKD-MBD, especially with respect to vascular calcification (VC).<sup>11–13</sup> In this context, Scl may be associated with detrimental clinical outcomes and could serve as a novel prognostic biomarker in patients undergoing MHD.

Indeed, several studies have demonstrated that elevated Scl can predict more CV events and higher mortality in patients with CKD;<sup>14,15</sup> however, other studies do not confirm this association.<sup>16,17</sup> A previous meta-analysis involving 1788 patients addressed this inconsistency; it found no significant associations between Scl level and all-cause or CV mortality.<sup>18</sup> However, in that meta-analysis, only three studies were pooled for all-cause mortality, while two studies were pooled for CV mortality or CV events; all studies exhibited high heterogeneity. Although that meta-analysis did not evaluate the relationships between Scl level and adverse clinical outcomes in patients undergoing MHD, recent studies have investigated these relationships. Among those studies, some revealed that a high Scl level was positively associated with fewer CV events and reduced mortality for patients undergoing MHD, suggesting that a high Scl level could serve as a predictor for clinical outcomes.<sup>14,19</sup> However, the results of other studies suggested that a low Scl level was predictive of fewer adverse outcomes,<sup>20,21</sup> or that Scl level failed to predict any outcomes in patients undergoing MHD.<sup>22,23</sup> Thus, the prognostic significance of Scl in patients undergoing MHD has not yet been determined. To better understand the predictive significance of Scl, we performed this systematic review and meta-analysis of the effects of different Scl levels on clinical outcomes (e.g. CV events and all-cause mortality) in patients undergoing MHD.

## Methods

### *Data source and literature search*

A comprehensive literature search was undertaken using electronic medical databases, including PubMed, Embase, Web of Science and Cochrane Library. All databases were thoroughly searched from the date of inception until December 20, 2019. The literature search

strategy was based on the PICOM format,<sup>24</sup> as shown in the following:

Is Scl level associated with adverse clinical outcomes in patients undergoing MHD?

**Patients:** Patients undergoing MHD

**Intervention:** Scl level

**Comparison:** High Scl level *versus* low Scl level

**Outcomes:** CV events or all-cause mortality

**Methods:** Prospective cohort studies

We searched the databases using combinations of the following medical terms: (“End stage renal disease” OR “ESRD” OR “end stage kidney disease” OR “ESKD” OR “uremia” OR “dialysis” OR “hemodialysis” OR “haemodialysis” OR “hemofiltration” OR “HD” OR “renal dialysis” OR “renal dialysis”) AND (“sclerostin” OR “Scl”) AND (“death” OR “mortality” OR “all-cause mortality” OR “total mortality” OR “morbidity” OR “cardiovascular event” OR “cardiovascular disease” OR “stroke” OR “coronary artery disease” OR “ischemic heart disease” OR “myocardial ischemia” OR “myocardial infarction” OR “prediction” OR “predictive” OR “endpoint” OR “outcome” OR “survival” OR “prognostic” OR “prognosis”). CV events included fatal or non-fatal CV events. All-cause mortality was defined as death from CV events or non-CV events.

### *Literature screening and quality assessment*

Studies were considered eligible if they met the following inclusion criteria: they used a prospective study design to investigate the association between Scl level and clinical outcomes in patients with CKD. However, studies were excluded if met the following exclusion criteria: they used a prospective study design and enrolled patients aged <18 years or dialysis vintage <months; they included patients who were undergoing pre-dialysis, peritoneal dialysis, or kidney transplantation; and/or they were not written in English or had no complete data. The quality of included prospective studies was evaluated using the Newcastle-Ottawa scale;<sup>25</sup> this score is determined based on three components:

participant selection, participant comparability and outcome assessment. Studies with a score  $\geq 7$  stars were considered to be of good quality.

#### *Data extraction and data analysis*

For eligible studies, we extracted the following data: first author's name, year of publication, region, participant number, baseline characteristics, Scl level, follow-up duration, outcomes, adjusted hazard ratios (HRs), relative risks, odds ratios (ORs) and 95% confidence indexes (CIs). If HRs were not directly extracted in a study, they were determined using Kaplan–Meier survival analysis, as previously described.<sup>26</sup> Meta-analysis was conducted for the total effect sizes and 95% CIs using RevMan 5.3.5 software (Cochrane Collaboration, Copenhagen, Denmark). Heterogeneities of studies were assessed using  $I^2$  statistics. A random-effects model was used when  $I^2 \geq 50\%$ . Sensitivity analysis was conducted by removing studies in a sequential manner. Publication bias was assessed by Begg's and Egger's tests, using Stata software 12.0 (Stata Corp, College Station, TX, USA). Origins of heterogeneity were investigated using subgroup analysis. Values of  $p < 0.05$  were considered as statistical significance.

## Results

#### *Description of literature search and study selection*

In total, 639 records were initially identified through database searches using the search criteria described in the Methods section; two additional records were retrieved from the reference lists of included studies. Of these 641 records, 19 studies were retrieved for detailed evaluation; 16 prospective cohort studies were eventually included in the current meta-analysis. After screening titles and abstracts, 625 records were discarded because of duplication or lack of relevance. The study selection process is presented in Figure 1.

#### *Characteristics of included studies*

Sixteen cohort studies with 3436 patients undergoing MHD were included in this meta-analysis.<sup>14,16,17,19–23,27–34</sup> These studies were prospectively designed and published from 2013 to 2019. Five studies were from Asia,<sup>14,20,29,32,34</sup> while the remaining 11 were from Europe. Thirteen studies

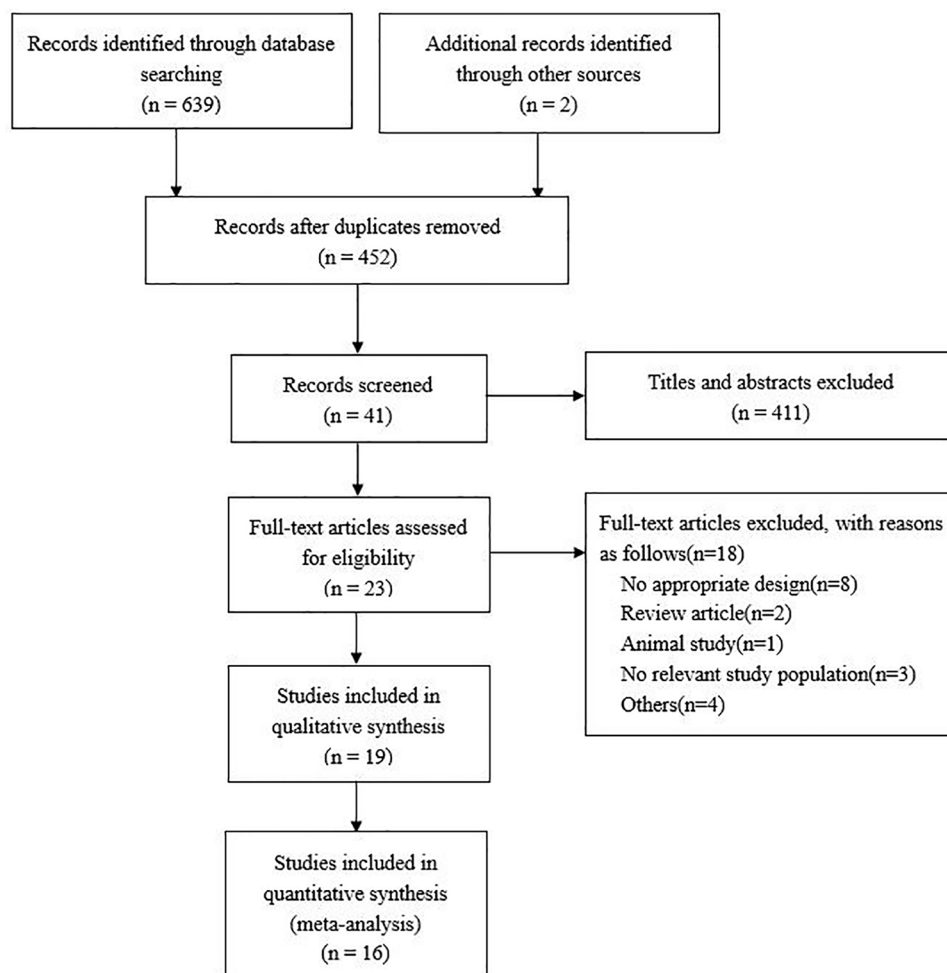
reported the mean dialysis vintages, while the remaining three did not.<sup>14,17,30</sup> Of the included studies, six reported both CV events and all-cause mortality,<sup>16,20,21,29,30,34</sup> three reported only CV events,<sup>14,23,32</sup> and seven reported only all-cause mortality.<sup>17,19,22,27,28,31,33</sup> The baseline characteristics are presented in Table 1. Based on the Newcastle–Ottawa scale, the average score was 6.6; nine and seven studies were graded as good and fair, respectively (Table 2).

#### *Relationship of Scl level with CV events*

In total, nine studies reported CV events, such as fatal and non-fatal CV events. Six studies reported adjusted HRs and 95% CIs (high Scl level *versus* low Scl level).<sup>14,16,21,29,30,34</sup> One study reported that a high Scl level was correlated with fewer CV events [Scl per 1 pmol/L increase, HR = 0.982 (95% CI, 0.967–0.996)];<sup>32</sup> we calculated its OR (high Scl level *versus* low Scl level) and included in our pooled analysis. The pooled HR was 0.8 (95% CI, 0.42–1.53), with significant heterogeneity ( $I^2 = 82\%$ ,  $p < 0.00001$ ; Figure 2). However, there was no significant publication bias (Begg's test  $p = 0.548$ , Egger's test  $p = 0.371$ ; Figure 3). The remaining two studies did not report adjusted HRs.<sup>20,23</sup> Because these two studies showed no relationship between Scl level and CV events in the crude model, they were not included in the meta-analysis. We presumed that our results were not affected by exclusion of these two studies, given that their findings were consistent with our pooled results. These results persisted in sensitivity analysis, following removal of any single study.

#### *Relationship of Scl level with all-cause mortality*

Of the 16 included studies, 13 reported all-cause mortality; seven of these reported adjusted HRs and 95% CIs (high Scl level *versus* low Scl level).<sup>16,19,27,29,30,33,34</sup> One study reported that a high Scl level was associated with higher all-cause mortality [Scl per 10 pmol/L increase, HR = 1.095 (95% CI, 1.022–1.174)];<sup>20</sup> another study reported that Ln Scl was associated with mortality [HR = 2.378 (95% CI, 1.108–5.104)].<sup>17</sup> We calculated the ORs (high Scl level *versus* low Scl level) from these two studies and included them with other HRs for our pooled analysis. The combined HR was 0.93 (95% CI, 0.56–1.54; Figure 4).



**Figure 1.** Study screening flow.

Although there was significant heterogeneity across the studies ( $I^2=83\%$ ,  $p<0.00001$ ; Figure 4), there was no evidence of significant publication bias (Begg's test  $p=1.000$ , Egger's test  $p=0.537$ ; Figure 5). The remaining four studies did not report adjusted HRs and 95% CIs. Because no relationship was found among the four studies in the crude models, their HRs were not retrieved or calculated for meta-analysis. As with all-cause mortality, we presumed that our results were not affected by exclusion of these four studies. These results persisted in sensitivity analysis, following removal of any single study.

#### Subgroup meta-analysis

To examine potential sources of heterogeneity, we performed independent subgroup meta-analysis across studies based on age, sample size,

follow-up time, dialysis vintage and region. For CV events, we found that age, dialysis vintage and region did not significantly influence heterogeneity. However, there was no significant heterogeneity in subgroups with larger sample size ( $\geq 200$ ) ( $I^2=26\%$ ,  $p=0.25$ ) and shorter follow-up period ( $<3$  years) ( $I^2=42\%$ ,  $p=0.18$ ; Table 3). In addition, in the subgroup with a shorter follow-up period, a high Scl level was associated with fewer CV events [pooled HR=0.44 (95% CI, 0.29–0.69)]. For all-cause mortality, we found that age, follow-up period and region did not significantly influence heterogeneity. However, there was no significant heterogeneity in subgroups with larger sample size ( $\geq 200$ ) ( $p=0.29$ ;  $I^2=20\%$ ) and shorter dialysis vintage ( $<50$  months) ( $p=0.13$ ;  $I^2=47\%$ ; Table 4). Moreover, a high Scl level was associated with reduced all-cause mortality in subgroups with larger sample size ( $\geq 200$ ) [pooled

**Table 1.** Characteristics of the included studies.

First author	Country	Number	HD vintage (month)	Follow-up period	Average age (year)	Versus	Outcomes	HR or OR and 95% CI	Conclusion
Kalousova <i>et al.</i> <sup>21</sup>	Prague	106 HD	26.5	5.0 years	61 ± 14	High versus low	CV mortality	3.251 (1.094–9.663)	Increased mortality
Jorgensen <i>et al.</i> <sup>16</sup>	Denmark	42 HD	14	3.7 years	58.13 ± 12	High versus low	Fracture	1.21 (0.47, 3.10)	No relationship
		17 PD					CV events	0.43 (0.18, 1.01)	
		98 CKD					All-cause mortality	0.56 (0.26–1.19)	
Gelir <i>et al.</i> <sup>23</sup>	Turkey	97HD	79 ± 60	27 months	55 ± 15	Overall Scl	CV events	Un:1.01 (1.00–1.04)	No relationship
Chen <i>et al.</i> <sup>20</sup>	China	84 HD	57.6 (27.3–85.5)	61.2 months	63.9 ± 11.5	Scl per 10 pmol/L increase:	All-cause mortality	1.095 (1.022–1.174)	Increased mortality
						High versus low	Indirect	3.857 (1.315–9.345)	
							CV mortality	Un:1.060 (0.993–1.167)	
Sato <i>et al.</i> <sup>34</sup>	Japan	389HD	37 (14–88)	42 months	67 (58–76)	High versus low	All-cause mortality	1.09 (0.56–2.14)	No relationship
							CV mortality	1.16 (0.42–3.34)	
Wang <i>et al.</i> <sup>14</sup>	China	53HD	>3	16 months	58.3 ± 13.4	High versus low	CV events	0.455 (0.31–0.66)	Reduced CV events
		35PD					AAC		
		30 CKD							
Lips <i>et al.</i> <sup>33</sup>	Netherlands	396HD	22 (11–40)	2.9 years	63.6 ± 13.9	High versus low	All-cause mortality	0.51 (0.31–0.86)	Reduced mortality
Kirkpantur <i>et al.</i> <sup>22</sup>	Turkey	350 HD	59 ± 30	24 months	55 ± 10	High versus low	All-cause mortality	None	No relationship
Jean <i>et al.</i> <sup>19</sup>	France	207 HD	57.2 ± 75	30 months	70.2 ± 14	High versus low	All-cause mortality	0.5 (0.25–0.93)	Reduced mortality
Nowak <i>et al.</i> <sup>31</sup>	Switzerland	239 HD	59 ± 53	1461 days	68 ± 14	Scl per SD increase:	All-cause mortality	1.02 (0.75–1.38)	No relationship

*(Continued)*

Table 1. (Continued)

First author	Country	Number	HD vintage (month)	Follow-up period	Average age (year)	Versus	Outcomes	HR or OR and 95% CI	Conclusion
Drechler <i>et al.</i> <sup>30</sup>	Netherlands	614 HD 59 PD	>3	1.5 or 4 year	63 ± 14	High versus low	All-cause mortality	0.39 [0.22–0.68] 0.60 [0.41–0.89]	Reduced mortality
							CV mortality		
							1.5 year: 4 years:	0.29 [0.13–0.62] 0.59 [0.35–0.98]	
Yang <i>et al.</i> <sup>32</sup>	Taiwan	125 HD	91	2 years	59 ± 12.3	Scl per 1 pmol/L increase;	CV events	0.982 [0.967–0.996]	Reduced CV events
							High versus low	0.195 [0.068–0.563]	
Gonçalves <i>et al.</i> <sup>29</sup>	Brazil	91 HD	120 [48–168]	10 years	42.3 ± 18.8	High versus low	All-cause mortality	2.2 [1.35–3.56]	Increased mortality
							CV mortality	2.88 [1.35–6.15]	
Desjardins <i>et al.</i> <sup>17</sup>	France	94 CKD	None	829 days	67 ± 12	Ln Scl	All-cause mortality	2.378 [1.108–5.104]	Increased mortality
							Indirect	2.593 [1.234–5.5452]	
Delanaye <i>et al.</i> <sup>28</sup>	Belgium	164 HD	22.5 [11–44]	2 years	74.0 [62.8–80.5]	High versus low	All-cause mortality	None	No relationship
Viaene <i>et al.</i> <sup>27</sup>	Belgium	100 HD	39.9 [15.7–68.8]	637 days	68 ± 13	High versus low	All-cause mortality	0.33 [0.15–0.73]	Reduced mortality

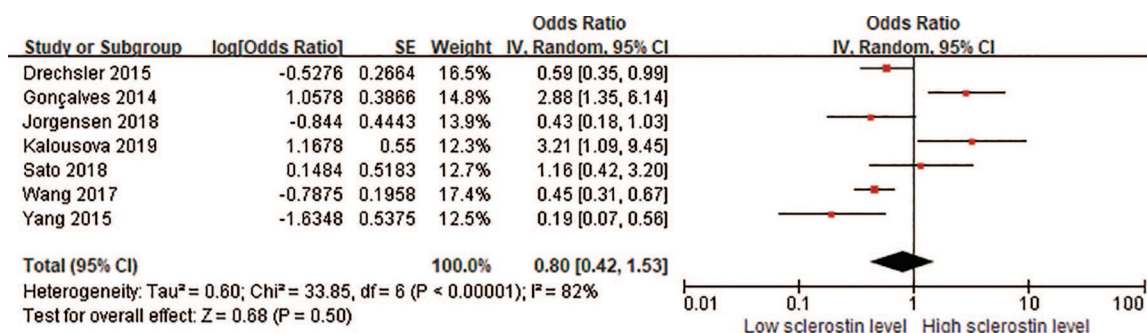
AAC, abdominal aortic calcification; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; HD, hemodialysis; HR, hazard ratio; OR, odds ratio; PD, peritoneal dialysis; Scl, sclerostin; Un: unadjusted.

**Table 2.** NOS scores of the included studies.

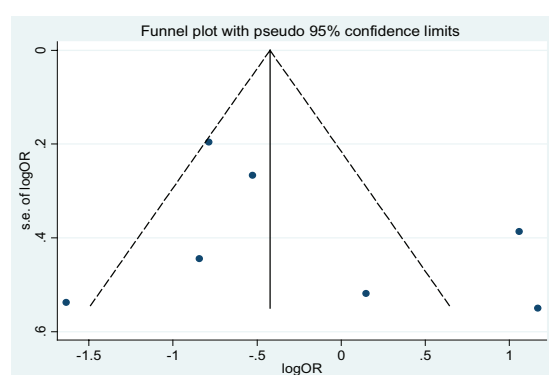
Cohort study	Selection		Comparability			Outcome		Total scores	
	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor*	Outcome assessment	Was follow-up long enough for outcomes to occur		Adequacy of follow-up of cohorts
Kalousova <i>et al.</i> <sup>21</sup>	/	☆	☆	☆	☆☆	☆	☆	/	7
Jorgensen <i>et al.</i> <sup>16</sup>	/	☆	☆	☆	/	☆	☆	/	5
Gelir <i>et al.</i> <sup>23</sup>	/	☆	☆	☆	/	☆	☆	/	4
Chen <i>et al.</i> <sup>20</sup>	/	☆	☆	☆	☆☆	☆	☆	/	7
Sato <i>et al.</i> <sup>34</sup>	☆	☆	☆	☆	☆☆	☆	/	☆	8
Wang <i>et al.</i> <sup>14</sup>	/	☆	☆	☆	☆☆	☆	/	/	6
Lips <i>et al.</i> <sup>33</sup>	☆	☆	☆	☆	☆☆	☆	/	☆	8
Kirkpantur <i>et al.</i> <sup>22</sup>	☆	☆	☆	☆	/	☆	/	☆	8
Jean <i>et al.</i> <sup>19</sup>	☆	☆	☆	☆	☆☆	☆	/	☆	8
Nowak <i>et al.</i> <sup>31</sup>	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Drechsler <i>et al.</i> <sup>30</sup>	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Yang <i>et al.</i> <sup>32</sup>	/	☆	☆	☆	☆☆	☆	/	/	6
Gonçalves <i>et al.</i> <sup>29</sup>	/	☆	☆	☆	☆☆	☆	☆	/	7
Desjardins <i>et al.</i> <sup>17</sup>	/	☆	☆	☆	☆	☆	/	/	5
Delanaye <i>et al.</i> <sup>28</sup>	/	☆	☆	☆	/	☆	/	/	4
Viaene <i>et al.</i> <sup>27</sup>	/	☆	☆	☆	☆	☆	/	/	5

\*2 stars could be awarded for this item.  
NOS, Newcastle-Ottawa Scale.





**Figure 2.** Forest plots of sclerostin levels and CV events. CI, confidence interval.



**Figure 3.** Funnel plot of sclerostin levels and CV events.

HR=0.62 (95% CI, 0.46–0.83)] and shorter dialysis vintage (<50 months) [pooled HR=0.58 (95% CI, 0.36–0.91); Table 4]. Thus, sample size, follow-up period and dialysis vintage were potential sources of heterogeneity in this study.

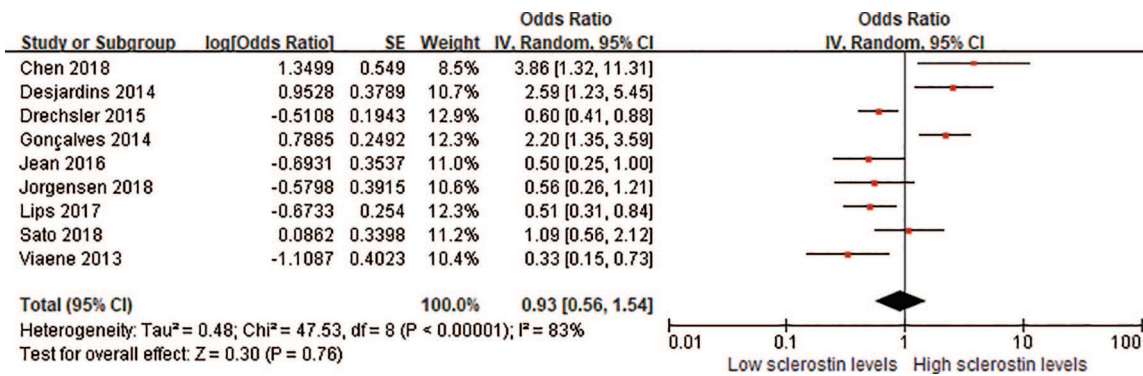
## Discussion

In this meta-analysis, we assessed the prognostic impact of Scl on CV events and all-cause mortality in patients undergoing prevalent haemodialysis. We found that Scl level failed to predict overall adverse clinical outcomes in this population, despite the better survival in the subgroup analysis. Our findings did not support the hypothesis that Scl may serve as a reliable predictor of clinical outcomes in this patient population.

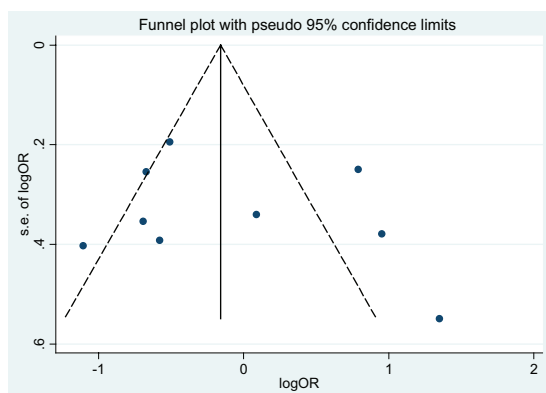
Scl is a bone-derived glycoprotein which serves as negative regulator of bone formation *via* inhibiting canonical Wnt/ $\beta$ -catenin signalling pathways.

Wnt/ $\beta$ -catenin pathways participate in various pathophysiological processes during embryonic development.<sup>35</sup> Wnt ligands can bind to Wnt co-receptors [i.e. lipoprotein receptor-related protein (LRP) 5 and LRP6] on the cell surface, thereby causing translocation of  $\beta$ -catenin from the cytoplasm to the nucleus. Then  $\beta$ -catenin interacts with DNA and activates the transcription of downstream target genes. Canonical Wnt signalling plays a pivotal role in osteogenesis by promoting osteoblast differentiation and activity.<sup>36</sup> Because Scl is an inhibitor of Wnt/ $\beta$ -catenin, it is presumably involved in bone metabolism. CKD-MBD is a common complication in patients undergoing MHD and is reportedly an independent predictor of poor survival outcome in this population. In particular, cumulative evidence demonstrated that Scl dysregulation was correlated with CKD-MBD in patients with CKD (e.g. VC, mineral metabolism disturbances and valve calcification).<sup>22,37–39</sup> Therefore, Scl is emerging as an important component of CKD-MBD.<sup>12</sup> Indeed, Scl levels were found to be increased in patients with early CKD; they were further increased in patients with advanced stages of CKD.<sup>15,40,41</sup> Furthermore, patients undergoing MHD have been found to exhibit higher Scl compared with patients who are not undergoing dialysis.<sup>16,17</sup> Therefore, disturbances in Scl levels may be linked to clinical outcomes in patients undergoing MHD. A previous meta-analysis assessed the prognostic role of Scl in patients with CKD; however, the findings were not statistically significant.<sup>18</sup> Notably, that meta-analysis included a relatively small number of studies and did not perform a subgroup analysis in patients undergoing MHD. Thus, the predictive role of Scl in this particular population has not been systematically evaluated.





**Figure 4.** Forest plots of sclerostin levels and all-cause mortality. CI, confidence interval.



**Figure 5.** Funnel plot of sclerostin levels and all-cause mortality.

In recent years, a growing number of studies have been conducted regarding the relationship between Scl level and clinical outcomes in patients undergoing MHD. Viaene *et al.* performed a prospective study to assess whether Scl level was predictive of clinical outcomes in 100 patients undergoing MHD who were followed up for 637 days.<sup>27</sup> They found that patients with Scl levels above the median value had reduced mortality, indicating that a high Scl level was associated with better survival. However, the association was absent in fully adjusted models. Subsequently, Drechsler *et al.* conducted a large cohort study to investigate the relationship between Scl level and mortality in 673 patients undergoing dialysis (91.2% were undergoing MHD). They found that a high Scl level predicted reduced CV or all-cause mortality at both 1.5 years and 4 years of follow-up.<sup>30</sup> Other studies demonstrated similar results.<sup>14,32,33</sup> In contrast, some studies showed that a high Scl level was

associated with increased CV or mortality.<sup>20,21,29</sup> Thus, it has remained unclear whether a high Scl level is protective or harmful in patients undergoing MHD. We conducted the current meta-analysis to address this inconsistency. Here, we included 16 studies with 3436 patients undergoing MHD. We found that, although subgroup analysis showed that patients in studies with shorter follow-up period or shorter dialysis vintage had reduced risks of adverse outcomes, a high Scl level was not associated with overall CV events or all-cause mortality in the final analysis despite inclusion of newer studies. Therefore, a high Scl level may not necessarily be an ideal predictor of clinical outcomes.

There are a few possible explanations for the negative findings. First, the effect of Scl on clinical outcomes in patients undergoing MHD may be partially related to VC. VC is regarded as a risk factor associated with increased mortality in patients undergoing pre-dialysis or dialysis.<sup>42,43</sup> VC is a process of mineral precipitation in the vasculature, which is similar to osteogenesis. Thus, it is reasonable to expect that Wnt signalling contributes to the VC process. Indeed, there is increasing evidence that Wnt signalling is enhanced in VC; notably, inhibition of Wnt signalling is followed by amelioration of VC.<sup>44–46</sup> Scl is an inhibitor of Wnt signalling, indicating that Scl may be a novel modulator of VC<sup>47</sup> and may affect clinical outcomes in patients undergoing MHD. However, clinical studies to test these hypotheses yielded controversial results. Some studies demonstrated inverse associations between Scl level and types of VC, such as aortic calcification,<sup>32</sup> aortic arch calcification<sup>34</sup> and abdominal aortic calcification.<sup>48</sup> These results suggested that Scl inhibited the VC process, similar to

**Table 3.** Results of subgroup analysis for CV events.

Subgroup	Studies	Effect estimate pooled HR (95% CI)	Heterogeneity within each group	Heterogeneity between subgroup
Age	7	0.80 (0.42, 1.53)		$p < 0.001$ ; $I^2 = 82\%$
Age $\geq 60$ years	3	1.20 (0.44, 3.24)	$p = 0.02$ ; $I^2 = 75\%$	
Age $< 60$ years	4	0.59 (0.22, 1.62)	$p < 0.001$ ; $I^2 = 87\%$	
Sample size	7	0.80 (0.42, 1.53)		$p < 0.0001$ ; $I^2 = 88\%$
Sample size $\geq 200$	2	0.71 (0.39, 1.30)	$p = 0.25$ ; $I^2 = 26\%$	
Sample size $< 200$	5	0.81 (0.30, 2.13)	$p < 0.0001$ ; $I^2 = 88\%$	
Follow-up period	7	0.80 (0.42, 1.53)		$p < 0.0001$ ; $I^2 = 82\%$
Follow-up period $\geq 3$ years	4	1.46 (0.56, 3.78)	$p = 0.005$ ; $I^2 = 77\%$	
Follow-up period $< 3$ years	3	0.44 (0.29, 0.69)	$p = 0.18$ ; $I^2 = 42\%$	
Dialysis vintage	5	0.99 (0.35, 2.82)		$p < 0.0001$ ; $I^2 = 84\%$
Dialysis vintage $\geq 3$ years	3	0.89 (0.19, 4.23)	$p = 0.0003$ ; $I^2 = 88\%$	
Dialysis vintage $< 3$ years	2	1.15 (0.16, 8.22)	$p = 0.004$ ; $I^2 = 88\%$	
Regions	7	0.80 (0.42, 1.53)		$p < 0.0001$ ; $I^2 = 82\%$
Asia	4	0.75 (0.26, 2.17)	$p < 0.0001$ ; $I^2 = 88\%$	
Not Asia	3	0.87 (0.32, 2.37)	$p = 0.01$ ; $I^2 = 78\%$	

CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

the inhibition of bone formation.<sup>12,49</sup> The inverse correlation could be explained as the increased apoptosis of vascular smooth muscle cells in VC led to reduced overall production of Scl.<sup>50</sup> The beneficial effects of Scl against VC may be responsible for the improved survival observed in some studies. However, other studies showed that Scl level was positively associated with abdominal aortic calcification,<sup>14</sup> valve calcification<sup>38,51</sup> and coronary artery calcification.<sup>39,52</sup> The extent of Scl expression in vessels or serum was strongly correlated with the degree of medial calcification in biopsy samples, indicating that a high Scl level was predictive of VC occurrence.<sup>39,53</sup> A plausible explanation for this positive relationship is that, as a defensive response or compensatory mechanism, a high Scl level might counteract the progression of VC.<sup>21,54</sup> Thus, although Scl has been implicated in the VC process, its exact effect on VC remains unclear. This uncertainty may contribute to inconsistent or even negative clinical outcomes.

A second possible explanation for the negative findings is that Scl measurement has not been standardised. Currently, three commercial ELISA kits are available from three manufacturers (Biomedica, TECO Medical and R&D Systems). However, the values of Scl determined by each kit were found to significantly differ in comparative studies.<sup>55,56</sup> These substantial differences in enzyme-linked immunosorbent assays inevitably influence the interpretation of findings regarding Scl in patients undergoing MHD. Standardisation of materials and protocols among Scl assays is necessary for clinical application of these assays. Recently, a novel automated chemiluminescent Scl assay, which exhibits a wide dynamic range and high specificity, has become commercially available; use of this assay may address the variability limitations of existing kits.<sup>57</sup>

A third possible explanation for the negative findings is that Scl can be cleared by haemodialysis

**Table 4.** Results of subgroup analysis for all-cause mortality.

Subgroup	Studies	Effect estimate pooled HR (95% CI)	Heterogeneity within each group	Heterogeneity between subgroup
Age	9	0.93 [0.56, 1.54]		$p < 0.0001$ ; $I^2 = 83\%$
Age $\geq 65$ years	4	0.83 [0.35, 1.96]	$p = 0.0007$ ; $I^2 = 82\%$	
Age $< 65$ years	5	1.01 [0.50, 2.05]	$p < 0.0001$ ; $I^2 = 87\%$	
Sample size	9	0.93 [0.56, 1.54]		$p < 0.0001$ ; $I^2 = 83\%$
Sample size $\geq 200$	4	0.62 [0.46, 0.83]	$p = 0.29$ ; $I^2 = 20\%$	
Sample size $< 200$	5	1.31 [0.55, 3.11]	$p < 0.0001$ ; $I^2 = 86\%$	
Follow-up period	9	0.93 [0.56, 1.54]		$p < 0.0001$ ; $I^2 = 83\%$
Follow-up period $\geq 3$ years	4	1.46 [0.70, 3.02]	$p = 0.006$ ; $I^2 = 76\%$	
Follow-up period $< 3$ years	5	0.66 [0.38, 1.14]	$p = 0.001$ ; $I^2 = 77\%$	
Dialysis vintage	7	0.86 [0.47, 1.60]		$p < 0.0001$ ; $I^2 = 83\%$
Dialysis vintage $\geq 50$ months	3	1.56 [0.50, 4.84]	$p = 0.0006$ ; $I^2 = 87\%$	
Dialysis vintage $< 50$ months	4	0.58 [0.36, 0.91]	$p = 0.13$ ; $I^2 = 47\%$	
Regions	9	0.93 [0.56, 1.54]		$p < 0.0001$ ; $I^2 = 83\%$
Asia	3	1.94 [1.04, 3.61]	$p = 0.10$ ; $I^2 = 57\%$	
Not Asia	6	0.64 [0.40, 1.03]	$p = 0.003$ ; $I^2 = 72\%$	

CI, confidence interval; HR, hazard ratio.

and subsequently detected in dialysate. A previous study showed that serum Scl concentration decreased remarkably during dialysis. Moreover, dialysis dose enhanced Scl clearance, whereas convection volume did not.<sup>58</sup> Another study showed that the Scl level in dialysate gradually increases during dialysis, whereas the plasma concentration remains relatively constant.<sup>59</sup> Thus, Scl is dialysable and its level is influenced by dialysis, which indicates that Scl levels cannot be compared among dialysis modalities. In addition, Scl levels in male subjects were higher than that in female ones in five included studies,<sup>21,23,27,31,34</sup> thus, differences in Scl levels regarding genders possibly influence the clinical outcomes. Finally, we found that PTH level increased as Scl level decreased in eight included studies,<sup>16,22,23,27,30–32,34</sup> and PTH was inversely correlated with Scl level. However, the effect of PTH on Scl or adverse outcomes had not been evaluated in most included

studies, which also influences the interpretation of the findings.

In total, our study showed that patients with a high Scl level tended to experience fewer CV events and tended to exhibit reduced all-cause mortality, which was also demonstrated in subgroup analysis. Longer duration of dialysis time was significantly associated with greater mortality risk in patients undergoing MHD.<sup>60</sup> Thus, the effects of Scl level on adverse outcomes may have been attenuated by longer follow-up period or dialysis vintage. Patients in the subgroup with larger sample size had shorter follow-up period or dialysis vintage. These possibly explained the inconsistent results in subgroup analysis. However, the results were not statistically significant in the final meta-analysis except for subgroup analysis. Thus, the available evidence does not support the hypothesis that Scl

is as an ideal prognostic biomarker for patients undergoing MHD. Inconsistent effects of Scl on VC, lack of standardisation in Scl measurement and differences in baseline characteristics or Scl levels may explain the negative findings. These issues should be addressed to determine whether Scl can be used as a clinical biomarker.

Several limitations should be addressed in this meta-analysis. First, the included studies exhibited high heterogeneity. Differences in methodologies among studies (e.g. sample size, follow-up period and dialysis vintage) may have contributed to the observed heterogeneity, which has been confirmed in the subgroup analysis. Second, subgroup analysis according to possible effect modifiers (e.g. follow-up time, sample size and dialysis modality) was not conducted in most included studies. Thus, the associations of Scl with clinical outcomes were not accurately evaluated among patient subgroups. Third, several adjusted HRs were not obtained or calculated, which may have influenced the results of this study. Finally, this meta-analysis included several studies with small sample sizes and short follow-up periods; these low-quality studies may have reduced the strength of our conclusions.

In conclusion, this meta-analysis showed no significant associations between Scl level and CV events or all-cause mortality in patients undergoing MHD. However, conclusions drawn in our study should be interpreted carefully due to inherent limitations regarding the included studies and inconsistent findings in the subgroup analysis. Thus, additional well-designed studies with large sample sizes are acquired to clarify the predictive performance of Scl in patients undergoing MHD.

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### Author contributions

SSL and QFL designed the study. SSL and ZQZ undertook the literature search. DWH and ALH extracted the data. QFL and ZQZ analysed the data. SSL and ALH wrote the manuscript. All authors reviewed, edited, and approved the final version of this manuscript.


### Conflict of interest statement

The authors declare that there is no conflict of interest.

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