REVIEW

Journal of Cachexia, Sarcopenia and Muscle 2022; **13**: 145–158
Published online 5 January 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12890

Diagnosis, prevalence, and mortality of sarcopenia in dialysis patients: a systematic review and meta-analysis

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Abstract

There is no consensus on the prevalence of sarcopenia or its impact on mortality in end-stage renal disease patients undergoing dialysis. This review aimed to summarize the diagnostic criteria of sarcopenia and its prevalence and impact on the mortality of end-stage renal disease patients undergoing dialysis. Embase, MEDLINE, PubMed, and Cochrane Library were searched from inception to 8 May 2021 to retrieve eligible studies that assessed muscle mass by commonly used instruments, such as dual-energy X-ray absorptiometry, bioelectrical impedance analysis, magnetic resonance imaging, and body composition monitor. Two assessment tools matched to study designs were employed to evaluate study quality. Pooled sarcopenia prevalence was calculated with 95% confidence interval (CI), and heterogeneity was estimated using the I^2 test. Associations of sarcopenia with mortality were expressed as hazard ratio (HR) and 95% CI. The search identified 3272 studies, and 30 studies (6162 participants, mean age from 47.5 to 77.5 years) were analysed in this review. The risk of bias in the included studies was low to moderate. Twenty-two studies defined sarcopenia based on low muscle mass (LMM) plus low muscle strength and/or low physical performance, while eight studies used LMM alone. Muscle mass was assessed by different instruments, and a wide range of cut-off points were used to define LMM. Overall, sarcopenia prevalence was 28.5% (95% CI 22.9–34.1%) and varied from 25.9% (I^2 = 94.9%, 95% CI 20.4–31.3%; combined criteria) to 34.6% (I^2 = 98.1%, 95% CI 20.9–48.2%; LMM alone) (P = 0.247 between subgroups). The statistically significant differences were not found in the subgroups of diagnostic criteria ($P > 0.05$) and dialysis modality ($P > 0.05$). Additionally, the sarcopenia prevalence could not be affected by average age [regression coefficient 0.004 (95% CI: −0.005 to 0.012), P = 0.406] and dialysis duration [regression coefficient 0.002 (95% CI −0.002 to 0.005), P = 0.327] in the meta-regression. The pooled analyses showed that combined criteria of sarcopenia were related to a higher mortality risk [HR 1.82 (I^2 = 26.3%, 95% CI 1.38–2.39)], as was LMM [HR 1.61 (I^2 = 26.0%, 95% CI 1.31–1.99)] and low muscle strength [HR 2.04 (I^2 = 80.4%, 95% CI 1.19–3.5)]. Although there are substantial differences in diagnostic criteria, sarcopenia is highly prevalent in dialysis patients and is linked to increased mortality. The standardization of sarcopenia diagnostic criteria would be beneficial, and future longitudinal studies are needed to investigate the prevalence and prognostic value of sarcopenia in dialysis patients.

Keywords Sarcopenia; Dialysis; Diagnosis; Prevalence; Mortality

Received: 24 July 2021; Revised: 3 November 2021; Accepted: 22 November 2021
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Introduction

With the development of renal replacement therapies, including peritoneal dialysis (PD), haemodialysis (HD), kidney transplantation, and continuous renal replacement therapy (which is often used for acute renal failure), patients with end-stage renal disease (ESRD) are routinely choosing treatment by PD, HD, and kidney transplantation to prolong their lifespan.[1] Because of the shortage of donor kidneys, PD and HD are increasingly chosen by patients with ESRD.

Existing literature suggests that sarcopenia is common among ESRD patients undergoing dialysis. Firstly, metabolic disorders and inflammation induced by kidney failure result in the development of sarcopenia. The former include nutritional deficiency, insulin resistance, diabetic nephropathy, acid–base imbalance, and electrolyte disorder.[2] The inflammatory processes mainly comprise the continuous release of pro-inflammatory cytokines and oxidation stress damage.[3] Secondly, dialysis procedures stimulate protein degradation and reduce protein synthesis; these responses persist following dialysis, which might lead to loss of muscle mass.[4,5]

In patients undergoing dialysis, sarcopenia appears to confer adverse health outcomes, for example, functional decline, physical falls, hospitalization, and even death.[6] Despite sarcopenia contributing to the poor prognosis of patients undergoing dialysis, the real clinical impact, especially related mortalities, has not been analysed. Furthermore, as the prevalence of sarcopenia in patients on dialysis has a wide range, its true impact on mortality is difficult to accurately ascertain.

One of the most important factors leading to the large variability in sarcopenia prevalence is the availability of different diagnostic criteria. There are more than four international recommended criteria, such as the diagnostic criteria developed by the European Working Group on Sarcopenia in Older People (EWGSOP),[7,8] Asian Working Group for Sarcopenia (AWGS),[9,10] Foundation for the National Institutes of Health Sarcopenia Project,[11] and International Working Group on Sarcopenia.[12]

Future intervention researches for sarcopenia in dialysis patients need an accurate estimate of prevalence. However, the prevalence of sarcopenia is affected by the large variability in diagnostic criteria and characteristics of patients and varies too widely (4[13]–68%[14]) to use for comparison. Therefore, we performed this review to provide a comprehensive picture of the diagnostic criteria and prevalence of sarcopenia in those treated by dialysis and interpret its predictive value in terms of overall mortality. We also conducted subgroup analysis and meta-regression (e.g. dialysis modality, age, and duration of dialysis) with an attempt to identify dialysis patients with high risk of sarcopenia; this endeavour could guide the selection of preventions for sarcopenia in dialysis patients.

Methodology

Inclusion and exclusion criteria

When performing this review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement (PRISMA 2020) principles,[15] which is an updated set of guidelines from PRISMA 2009.[16] To be included, a study was required to meet five specific criteria: (i) conducted on adults with ESRD who received dialysis treatment; (ii) provided prevalence data for sarcopenia in patients undergoing dialysis; (iii) defined sarcopenia as the presence of low muscle mass (LMM) plus low muscle strength (LMS), and/or low physical performance (LPP), or LMM alone; (iv) detected muscle mass with instruments commonly used previous to the study, for example, dual-energy X-ray absorptiometry, bioelectrical impedance analysis, magnetic resonance imaging, and bioelectrical impedance spectroscopy; and (v) study types were cross-sectional or retrospective or prospective.

Studies were excluded based on the following criteria: (i) sarcopenia diagnostic criteria were not reported; (ii) animal studies, reports, editorials, reviews, comments, or conference abstracts; and (iii) published in languages other than English.

Outcomes

The main outcomes of this review were (i) the methods used to diagnose sarcopenia, including diagnostic items, techniques for measurement, and sarcopenia threshold values, and (ii) sarcopenia prevalence in patients treated with dialysis and (iii) the impact of combined criteria (LMM plus LMS and/or LPP), LMM, LMS, and LPP on mortality in dialysis patients.

Study databases and searching strategy

Using Ovid SP, we systematically screened relevant articles published up to 8 May 2021 from the databases Embase, MEDLINE, PubMed, and Cochrane Library without language restrictions. The detailed search strategy is shown in Supporting Information, *Table* S1. We also screened the citations included in the articles found in the database search for additional pertinent studies.

Study selection

Two reviewers (X. S. and T. L.) screened the title and abstract of each search result independently while following the eligibility criteria to select possible studies for inclusion. Then, X. S. and T. L. separately reviewed the full text of these studies and decided on the final studies for inclusion. Lastly,

DOI: 10.1002/jcsm.12890

X. S. and T. L. independently screened the citations used in the included papers to identify other studies meeting the search criteria. Any disagreement in study selection was resolved by discussing with a third, independent, reviewer (J. Y.). When the data used in two or more studies came from the same cohort, those with the largest sample size were included in the analysis.

Data extraction

Two reviewers (X. S. and Y. Z.) extracted the data independently using standardized templates suitable for research objectives. A third assessor (J. Y.) reviewed the data-extraction steps, and any disagreements were discussed and resolved. The following variables were collected using a data collection form: name of the first author, publication date, country, study design, sample size, proportion of men, mean age, dialysis method, duration of dialysis, diagnostic method for sarcopenia, skeletal muscle mass assessment technique, prevalence of sarcopenia, and sarcopenia diagnostic criteria. Meanwhile, if possible, the hazard ratio (HR) and 95% confidence interval (CI) for the overall mortality associated with the combined criteria (LMM plus LMS and/or LPP), LMM, LMS, and LPP were extracted.

Assessing the risk of bias in the selected studies

The risk of bias in the studies selected for the review was separately estimated by X. S. and Y. Z. using the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies—a validated procedure that assesses the quality of cohort and cross-sectional studies[17] that includes 14 items that are applied to estimate selection, information, and measurement biases as well as confounding. Additionally, we selected a tool that was designed specifically for assessing the risk of bias in prevalence studies and has been proved to have high interrater agreement.[18] Ten items were used to address three domains of potential bias: measurement, selection, and analysis. A score of 8 or more was defined as low risk, 6 or 7 was considered moderate risk, and 5 or less was a high risk of bias. The arbitrator (J. Y.) was called upon to resolve disagreements among the reviewers.

Data analyses

Statistical analyses were carried out with STATA/MP (Version 14.0, StataCorp, College Station, TX, USA), and forest plots were created to visualize the results. Heterogeneity was estimated by the I^2 test, with I^2 cut-off values of 25%, 50%, and 75% respectively representing low, medium, and high heterogeneity.[19] We applied a random-effects model to calculate the pooled sarcopenia prevalence with a 95% CI when the I^2 index was interpreted as suggesting high heterogeneity; otherwise, the fixed-effects model was used. In studies that evaluated sarcopenia by multiple diagnostic criteria, the prevalence most resembling the EWGSOP (2010) recommendation was pooled in the meta-analysis. Additionally, to ascertain the impact of sarcopenia on mortality, the HR and 95% CI of the combined criteria (LMM plus LMS and/or LPP), LMM, LMS, and LPP were retrieved for meta-analysis if possible. When we could extract HR and 95% CI from both univariate and multivariate analyses, the data from multivariate analyses were retrieved for meta-analysis. Moreover, when both crude and adjusted HR and 95% CI were reported, adjusted HR and 95% CI were selected for data synthesis.

To investigate the possible reasons for heterogeneity, we performed subgroup analyses and meta-regression on diagnostic criteria, dialysis modality, average age, and duration of dialysis. Sensitivity analysis was conducted to evaluate the quality and congruity of the results by deleting one study at a time. Publication bias was evaluated with the Egger test[20] and Begg test[21] ($P < 0.05$).

Results

Study selection

Figure 1 depicts the flow chart of the literature selection process. In all, 3272 records were collated from the database search. After removing duplicates, 2402 titles and abstracts were screened, resulting in 65 relevant studies for full-text screening, which resulted in 29 of these studies being included in our review. We also found an additional article after screening the reference lists of these 29 studies. The reasons used to exclude some articles subsequent to the full-text screening were shown in the flow chart and *Table* S2. Finally, we selected 30 articles, involving 6162 participants, that satisfied with all inclusion criteria for the systematic review and meta-analysis.

Study characteristics

The characteristics of the included studies are summarized in *Table* 1. The 30[13,14,22–49] studies enrolled 6162 individuals who were included in the qualitative analysis. All of the included studies were published after 2013. Of these, 11 adopted a cross-sectional design, 6 reported retrospective data, and 13 were prospective cohort studies. Twenty studies were conducted in HD populations, and 10 were conducted in PD populations. The mean age of the study participants ranged from 47.5 to 77.5 years, and the mean duration of dialysis ranged from 3 to 91.7 months. The included patients were sampled from a diversity of populations, including 14

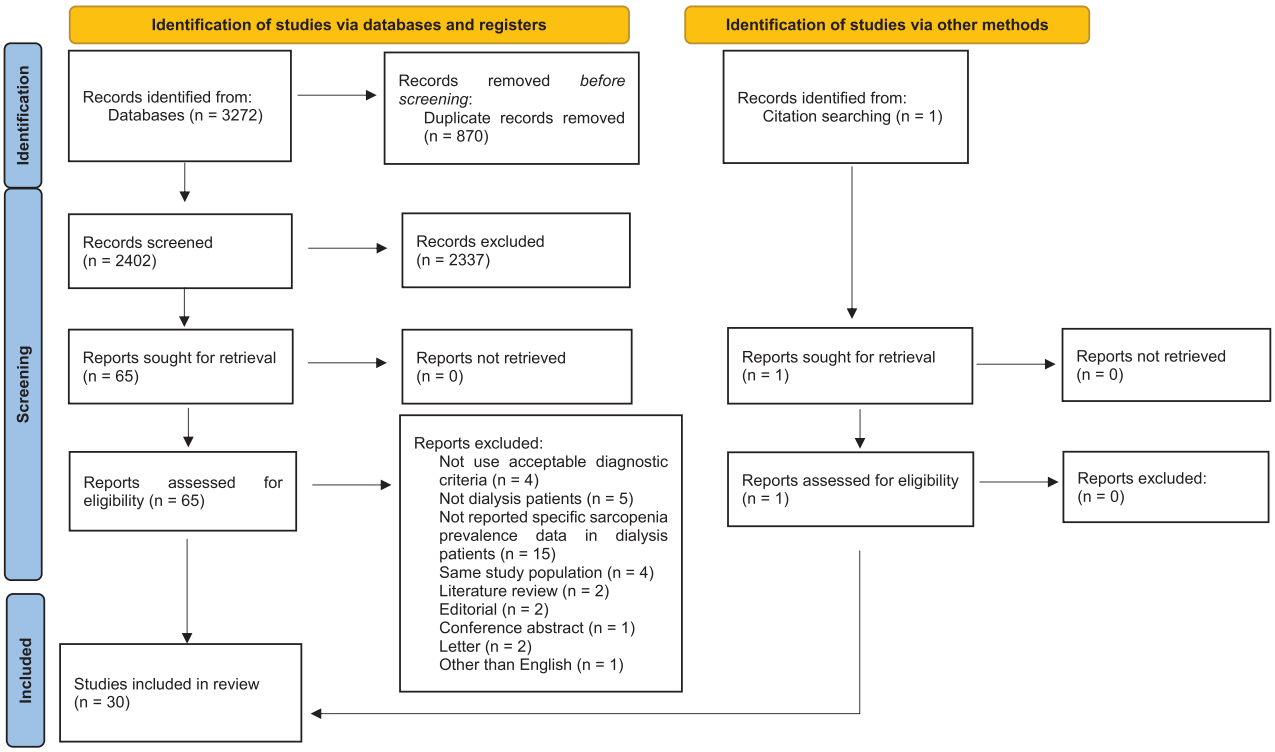

Figure 1 The flow chart of the literature selection.

studies conducted in Asia, 8 in America, and 8 in Europe (*Table* 1).

Risk of bias in the included studies

The overall quality of included studies was moderate when assessed by the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies[17] (full details in *Figure* S1). Similarly, when appraised by prevalence studies assessment, 16 studies classed as moderate risk of bias studies and 14 classed as low risk of bias studies[18] (*Figure* S2).

Diagnostic method and prevalence of sarcopenia in dialysis patients

Table 2 summarized the commonly used diagnostic criteria of sarcopenia. Twenty-two studies defined sarcopenia by LMM plus LMS and/or LPP, 17 of them defined sarcopenia by EWGSOP criteria, and 4 of them defined sarcopenia by AWGS criteria. Eight studies used only LMM to diagnose sarcopenia. Different measurement methods and cut-off values were utilized to identify LMM, LMS, and LPP in these studies (*Table* 3). Muscle mass assessments were conducted with dual-energy X-ray absorptiometry (17 studies), bioelectrical impedance analysis (8 studies), and bioelectrical impedance spectroscopy (5 studies), and more than 10 cut-off points were used to identify LMM. Muscle strength was assessed by handgrip dynamometry; the cut-off points for identifying LMS varied from 16 to 20.7 kg in women and 26 to 36.6 kg in men. Physical performance was detected by walk tests with different walking distance, ranging from 4 to 10 m; the cut-off points for identifying LPP were a gait speed <0.8 or <1.0 m/s.

In the 30 studies included, sarcopenia prevalence wide ranged from 4% to 68% (*Table* 1), and the pooled estimated prevalence was 28.5% (I^2 = 96.7%, 95% CI 22.9–34.1%; *Figure* 2).

Subgroup analysis: sarcopenia definition, diagnostic criteria, and dialysis modality

The prevalence of sarcopenia in studies only using LMM [34.6% (I^2 = 98.1%, 95% CI 20.9–48.2%, 8 studies, 2101 cases)] were seemly higher than those defining sarcopenia using combined criteria [LMM plus LMS and/or LPP, 25.9% (I^2 = 94.9%, 95% CI 20.4–31.3%, 22 studies, 4061 cases)]; however, the difference did not exhibit statistical significance

Table 1 Characteristics of the included studies and main findings

First author and year	Country	Study design	Sample size	Male, *n* (%)	Female, *n* (%)	Mean age (years)[a]	Dialysis method	Duration of dialysis (months)[a]	Prevalence of sarcopenia			Criteria (assessment method to detect sarcopenia)	HGS measure hand	Muscle mass measure time	Sarcopenia diagnostic criteria
									Total, *n* (%)	Male, *n* (%)	Female, *n* (%)				
Lamarca (2014)[22]	Brazil	Cross-sectional	102	75	27	70.7	HD	27	13 (12.7%)	—	—	LMM (BIA) LMS (HGS)	Non-fistula hand	After dialysis	EWGSOP (2010)
Isoyama (2014)[23]	Brazil	Prospective cohort	330	203	127	53	HD	—	66 (20.0%)	—	—	LMM (DXA) LMS (HGS)	Dominant hand or non-fistula hand	After dialysis	EWGSOP (2010)
Ren (2016)[24]	China	Prospective observational	131	80	51	49.4	HD	71.3	18 (13.7%)	12 (15.0%)	6 (11.8%)	LMM (BIA) LMS (HGS)	Non-fistula hand	Before dialysis	EWGSOP (2010)
Bataille (2017)[25]	France	Cross-sectional	111	65	46	77.5	HD	28.4	35 (31.5%)	25 (38.5%)	10 (21.7%)	LMM (BIA) LMS (HGS)	Dominant hand	—	EWGSOP (2010)
Greenhall (2017)[26]	UK	Retrospective	490	—	—	55.3	PD	3	172 (35.1%)	—	—	LMM (BIA)	—	—	Others[b]
Jin (2017)[27]	China	Prospective cohort	117	57	60	60.8	PD	13.5	10 (8.6%)	—	—	LMM (BIA)	—	With peritoneal dialysate	Others[b]
Kamijo (2018)[28]	Japan	Prospective cohort	119	84	35	66.8	PD	—	13 (10.9%)	11 (13.1%)	2 (5.7%)	LMM (BIA) LMS (HGS) LPP (10mGS)	Dominant hand	—	AWGS (2014)
Kang (2017)[29]	Korea	Prospective cohort	631	341	290	53.2	PD	—	303 (48.0%)	175 (51.3%)	128 (44.1%)	LMM (DXA)	—	After drained out peritoneal dialysate	Others[b]
Kittiskulnam (2017)[30]	USA	Prospective cohort	645	378	267	56.7	HD	33.6	90 (14.0%)	53 (14.0%)	37 (13.9%)	LMM (BIS) LMS (HGS) LPP (4.6mGS)	Non-fistula hand	Before dialysis	EWGSOP (2010)
Malhotra (2017)[31]	USA	Retrospective	122	76	46	47.5	HD	31	58 (47.5%)	47 (61.8%)	11 (23.9%)	LMM (DXA)		Non-dialysis day	Others[b]
Abro (2018)[32]	UK	Retrospective	155	95	60	63.0	PD	9	17 (11.0%)	—	—	LMM (BIA) LMS (HGS)	Dominant hand	After drained out peritoneal dialysate	EWGSOP (2010)
As'habi (2018)[33]	Iran	Cross-sectional	79	35	44	—	PD	—	9 (11.4%)	8 (22.9%)	1 (2.3%)	LMM (BIA) LMS (HGS) LPP (4mGS)	—	After drained out peritoneal dialysate	EWGSOP (2010)
Dierkes (2018)[34]	Norway	Cross-sectional	24	17	7	63	HD	48	10 (41.7%)	—	—	LMM (BIA) LMS (HGS)	—	After dialysis	EWGSOP (2010)
Giglio (2018)[35]	Brazil	Prospective observational	170	111	59	70	HD	34.8	62 (36.5%)	52 (46.8%)	10 (16.9%)	LMM (DXA) + formula LMS (HGS)	Non-fistula hand	After dialysis	EWGSOP (2010)
Lin (2018)[36]	China	Cross-sectional	120	63	57	63.33	HD	56.52	20 (16.7%)	10 (15.9%)	10 (17.5%)	LMM (BIA) LMS (HGS) LPP (5mGS)	Non-fistula hand	—	EWGSOP (2010)

(*Continues*)

Table 1 (continued)

First author and year	Country	Study design	Sample size	Male, *n* (%)	Female, *n* (%)	Mean age (years)[a]	Dialysis method	Duration of dialysis (months)[a]	Prevalence of sarcopenia			Criteria (assessment method to detect sarcopenia)	HGS measure hand	Muscle mass measure time	Sarcopenia diagnostic criteria
									Total, *n* (%)	Male, *n* (%)	Female, *n* (%)				
Yoowannakul (2018)[37]	UK	Retrospective	600	373	227	66.3	HD	30.9	228 (38%)	154 (41.3%)	74 (32.6%)	LMM (BIA) LMS (HGS)	Dominant hand	After dialysis	EWGSOP (2010)
Yoowannakul (2018)[38]	UK	Retrospective	434	239	195	56	PD	3	205 (47.2%)	132 (55.2%)	73 (37.4%)	LMM (BIA)	—	After drained out peritoneal dialysate	Others[b]
Chiang (2019)[39]	USA	Prospective cohort	440	440	—	56.16	HD	32.4	75 (17.0%)	75 (17.0%)	—	LMM (BIS) LMS (HGS)	Both hands	Before dialysis	EWGSOP (2010)
Guida (2019)[43]	Italy	Cross-sectional	88	59	29	53.4	PD	15.9	39 (44.3%)	22 (37.3%)	17 (58.6%)	LMM (BIA)	—	After drained out peritoneal dialysate	Others[b]
Kim (2019)[40]	Korea	Prospective observational	142	81	61	59.8	HD	50.23	47 (33.1%)	24 (29.6%)	23 (37.7%)	LMM (BIS) LMS (HGS)	Non-fistula hand	—	EWGSOP (2010)
Lin (2020)[41]	China	Prospective cohort	126	65	61	63.2	HD	55.4	17 (13.5%)	9 (13.8%)	8 (13.1%)	LMM (BIS) LMS (HGS) LPP (6mGS)	Non-fistula hand	Before dialysis	EWGSOP (2010)
Mori (2019)[42]	Japan	Prospective cohort	308	185	123	58.06	HD	77.3	124 (40.3%)	69 (37.3%)	55 (44.7%)	LMM (DXA) LMS (HGS)	Both hands	After dialysis	AWGS (2014)
da Silva (2019)[13]	Brazil	Cross-sectional	50	24	26	55.74	PD	9.5	2 (4.0%)	—	—	LMM (DXA) LMS (HGS) LPP (4mGS)	—	—	EWGSOP (2010)
Kim (2020)[46]	Korea	Retrospective	160	109	51	55.1	PD	21.8	22 (13.8%)	—	—	LMM (BIS) LMS (HGS)	Dominant hand	—	Others[b]
Medeiros (2020)[44]	Brazil	Cross-sectional	92	—	—	63.3	HD	—	50 (54.3%)	—	—	LMM (BIA) LMS (HGS) LPP (4mGS)	Non-fistula hand	After dialysis	EWGSOP (2010)
Slee (2020)[45]	UK	Cross-sectional	87	63	24	61.68	HD	65.9	38 (43.7%)	—	—	LMM (BIA) LMS (HGS)	—	After dialysis	EWGSOP (2010)
Song (2020)[47]	Korea	Prospective observational	88	50	38	60.6	HD	50.8	36 (40.9%)	—	—	LMM (BIS)	Non-fistula hand	—	Others[b]
Matsuzawa (2021)[14]	Japan	Cross-sectional	50	29	21	77.5	HD	38.5	34 (68%)	21 (72.4%)	13 (61.9%)	LMM (BIA) LMS (HGS) LPP (4mGS)	Both hands	After dialysis	AWGS (2019)
Miyazaki (2021)[48]	Japan	Cross-sectional	20	14	6	76.5	HD	91.7	11 (55%)	—	—	LMM (DXA) LMS (HGS) LPP (6mGS)	—	—	AWGS (2019)
Takata (2021)[49]	Japan	Prospective observational	131	88	43	66.9	HD	—	8 (6.1%)	4 (4.5%)	4 (9.3%)	LMM (BIA)	—	—	Others[b]

AWGS, Asian Working Group for Sarcopenia; BIA, bioelectrical impedance analysis; BIS, bioelectrical impedance spectroscopy; DXA, dual-energy X-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older People; HGS, handgrip strength; LMM, lower muscle mass; LMS, lower muscle strength; LPP, lower physical performance.
[a]Mean or median as reported.
[b]Sarcopenia diagnostic criteria other than EWGSOP (2010), EWGSOP (2019), AWGS (2014), and AWGS (2019).

Table 2 Diagnostic criteria of sarcopenia

	Low muscle mass (ASM)	Low muscle strength (HGS)	Lower physical performance (GS)	Sarcopenia diagnosis
AWGS (2014)	ASM/height^2 <7.0 kg/m^2 for men and <5.4 kg/m^2 for women by using DXA ASM/height^2 <7.0 kg/m^2 for men and <5.7 kg/m^2 for women by using BIA	HGS < 26 kg for men and <18 kg for women	Usual gait speed <0.8 m/s for both sexes	Sarcopenia: LMM plus LMS and/or LPP
AWGS (2019)	ASM/height^2 <7.0 kg/m^2 for men and <5.4 kg/m^2 for women by using DXA ASM/height^2 <7.0 kg/m^2 for men and <5.7 kg/m^2 for women by using BIA	HGS < 28 kg for men and <18 kg for women	Usual gait speed <1.0 m/s for both sexes	Possible sarcopenia: LMS or LPP Sarcopenia: LMM plus LMS or LPP Severe sarcopenia: LMM plus LMS and LPP
EWGSOP (2010)	ASM/height^2 <7.26 kg/m^2 for men and <5.5 kg/m^2 for women	HGS < 30 kg for men and <20 kg for women	Usual gait speed ≤0.8 m/s for both sexes	Pre-sarcopenia: LMM Sarcopenia: LMM plus LMS or LPP Severe sarcopenia: LMM plus LMS and LPP
EWGSOP (2019)	ASM/height^2 <7.0 kg/m^2 for men and <5.5 kg/m^2 for women	HGS < 27 kg for men and <16 kg for women	Usual gait speed ≤0.8 m/s for both sexes	Possible sarcopenia: LMS Sarcopenia: LMM plus LMS Severe sarcopenia: LMM plus LMS and LPP
FINH	ALM/BMI < 0.789 for men and <0.512 for women	HGS < 26 kg for men and <16 kg for women	—	Sarcopenia: LMM plus LMS
IWGS	ASM/height^2 <7.23 kg/m^2 for men and <5.67 kg/m^2 for women	—	Usual gait speed <1.0 m/s for both sexes	Sarcopenia: LMM plus LPP

ALM/BMI, appendicular lean mass/body mass index; ASM, appendicular skeletal muscle; AWGS, Asian Working Group for Sarcopenia; BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health Sarcopenia Project; GS, gait speed; HGS, handgrip strength; IWGS, International Working Group on Sarcopenia; LMM, lower muscle mass; LMS, lower muscle strength; LPP, lower physical performance.

(P = 0.247, *Figure* S3). Additionally, the prevalence of sarcopenia defined by EWGSOP criteria [23.4% (I^2 = 94.2%, 95% CI 17.8–29.0%, 17 studies, 3404 cases)] was lower than the prevalence defined by AWGS criteria [42.6% (I^2 = 96.9%, 95% CI 18.7–66.6%, 4 studies, 497 cases)] and other criteria [32.2% (I^2 = 98.0%, 95% CI 19.6–44.8%, 9 studies, 2261 cases)]; however, the difference was not statistically significant (P = 0.165, *Figure* S3). Similarly, the prevalence of sarcopenia was revealed to be higher in HD populations [31% (I^2 = 95.5%, 95% CI 24.7–37.3%, 20 studies, 3839 cases)] than PD populations [23.4% (I^2 = 98.0%, 95% CI 11.9–34.9%, 10 studies, 2323 cases)]; however, the difference was not statistically significant (P = 0.255, *Figure* S3).

Meta-regression: average age and duration of dialysis

The pooled data on average age showed that it did not affect sarcopenia prevalence in the meta-regression [regression coefficient 0.004 (95% CI: −0.005 to 0.012), P = 0.406, 29 studies, 6083 cases] (*Figure* S4). Additionally, the effect size could not be predicted using the duration of dialysis in the meta-regression [regression coefficient 0.002 (95% CI −0.002 to 0.005), P = 0.327, 24 studies, 4780 cases] (*Figure* S5).

Impact of combined criteria (low muscle mass plus low muscle strength and/or low physical performance), low muscle mass, and low muscle strength on mortality

Data from 10 studies were available to meta-analyse mortality (*Table* 4). Patients who were diagnosed with sarcopenia by combined criteria (LMM plus LMS and/or LPP) had, on average, a higher risk of mortality than those without sarcopenia [HR 1.82 (I^2 = 26.3%, 95% CI 1.38–2.39), 6 studies, 1683 cases, *Figure* S6] and those diagnosed via LMM [HR 1.61 (I^2 = 26%, 95% CI 1.31–1.99), 8 studies, 2319 cases, *Figure* S7]. The fixed-effect model was chosen because of the consistency between studies for the earlier associations. Moreover, patients with LMS were also confirmed to have a higher risk of mortality [HR 2.04 (I^2 = 80.4%, 95% CI 1.19–3.5), 6 studies, 1566 cases, *Figure* S8] than those possessing normal muscle strength. For the relationship between LMS and the risk of mortality, the random-effects model was chosen, as suitable for the high between-study heterogeneity (I^2 = 80.4%).

Table 3 The details of diagnostic criteria and cut-off points of each study

Low muscle mass		References
BIA	1. EWGSOP (2010) Janssen *et al*. (2004)[69]: SMI < 10.76 kg/m^2 for men and <6.76 kg/m^2 for women	Ren *et al*. (2016),[24] Lin *et al*. (2018),[36] As'habi *et al*. (2018),[33] Lin *et al*. (2020),[41] Medeiros *et al*. (2020),[44] Slee *et al*. (2020),[45] Malhotra *et al*. (2017),[31] Greenhall *et al*. (2017)[26]
	2. EWGSOP (2010) Chien *et al*. (2008)[70]: MMI < 8.87 kg/m^2 for men and <6.42 kg/m^2 for women	Bataille *et al*. (2017),[25] Dierkes *et al*. (2018)[34]
	3. EWGSOP (2010) Newman *et al*. (2003)[71]: ASMI < 7.23 kg/m^2 for men and <5.67 kg/m^2 for women	Yoowannakul *et al*. (2018),[37] Abro *et al*. (2018)[32]
	4. EWGSOP (2010) Baumgartner *et al*. (1998)[72]: SMI ≥ 2 SD below sex-specific means of healthy young adults	Yoowannakul *et al*. (2018)[38]
	5. EWGSOP (2010)[73]: LBMI > 2 SD below means of young individuals (men: <15.9 kg/m^2; women: <12.8 kg/m^2)	Lamarca *et al*. (2014)
	6. EWGSOP (2010) Janssen *et al*. (2002)[74]: SM/BW < 37% for men and <28% for women	Guida *et al*. (2019)[43]
	7. AWGS (2014 or 2019)[9,10]: SMI < 7.0 kg/m^2 for men and 5.7 kg/m^2 for women	Jin *et al*. (2017),[27] Kamijo *et al*. (2018),[28] Matsuzawa *et al*. (2021),[14] Takata *et al*. (2021)[49]
DXA	1. EWGSOP (2010) Baumgartner *et al*. (1998)[72]: ASMI < 7.3 kg/m^2 in men and <5.5 kg/m^2 in women	Isoyama *et al*. (2014),[23] Giglio *et al*. (2018),[35] da Silva *et al*. (2019)[13]
	2. AWGS (2014)[9]: SMI < 7.0 kg/m^2 for men and 5.4 kg/m^2 for women	Mori *et al*. (2019),[42] Miyazaki *et al*. (2021)[48]
	3. FNIH[11]: ALM/BMI < 0.789 for men and <0.512 for women	Kang *et al*. (2017)[29]
BIS	1. EWGSOP (2010) Janssen *et al*. (2004)[69]: muscle mass of ≥2 SD below sex-specific means of healthy young adults	Kittiskulnam *et al*. (2017),[30] Chiang *et al*. (2019),[39] Kim *et al*. (2019)[40]
	2. Marcelli *et al*. (2015)[75]: LTI below the 10th percentile of a reference population	Kim *et al*. (2020),[46] Song *et al*. (2020)[47]
Low muscle strength		**References**
HGS	1. EWGSOP (2010) Lauretani *et al*. (2003)[76]: HGS < 30 kg for men and <20 kg for women	Isoyama *et al*. (2014),[23] Ren *et al*. (2016),[24] Bataille *et al*. (2017),[25] Dierkes *et al*. (2018),[34] Giglio *et al*. (2018),[35] Yoowannakul *et al*. (2018),[37] Lin *et al*. (2018),[36] Abro *et al*. (2018),[32] Kim *et al*. (2019),[40] da Silva *et al*. (2019),[13] Lin *et al*. (2020),[41] Medeiros *et al*. (2020),[44] Slee *et al*. (2020),[45] Song *et al*. (2020)[47]
	2. AWGS (2014)[9]: HGS < 26 kg for men and <18 kg for women	Kamijo *et al*. (2018),[28] As'habi *et al*. (2018),[33] Chiang *et al*. (2019),[39] Mori *et al*. (2019)[42]
	3. AWGS (2019)[10]: HGS < 28 kg for men and <18 kg for women	Miyazaki *et al*. (2021)[48]
	4. FINH[11]: HGS < 26 kg for men and <16 kg for women	Kittiskulnam *et al*. (2017)[30]
	5. Kim *et al*. (2018)[77]: HGS < 28.9 kg in men and <16.8 kg in women	Kim *et al*. (2020)[46]
	6. Schlüssel *et al*. (2008)[78]: HGS < 10th percentile of young individuals (men: right <36.6 kg and left <34.7 kg; women: right <20.7 kg and left <20.1 kg)	Lamarca *et al*. (2014)[22]
	Lower physical performance	**References**
4mGS	1. AWGS (2014) and EWGSOP (2010) Lauretani *et al*.[76]: GS < 0.8 m/s	As'habi *et al*. (2018),[33] da Silva *et al*. (2019),[13] Medeiros *et al*. (2020),[44] Matsuzawa *et al*. (2021)[14]
4.6mGS	1. FNIH[11]: walking speed <0.8 m/s	Kittiskulnam *et al*. (2017)[30]
5mGS	1. EWGSOP (2010) GS < 1.0 m/s	Lin *et al*. (2018)[36]
6mGS	1. EWGSOP (2010) GS < 0.8 m/s	Lin *et al*. (2020),[41] Miyazaki *et al*. (2021)[48]
10mGS	1. AWGS (2014) GS < 0.8 m/s	Kamijo *et al*. (2018)[28]

ALM/BMI, appendicular lean mass/body mass index; ASMI, appendicular skeletal muscle index; AWGS, Asian Working Group for Sarcopenia; BIA, bioelectrical impedance analysis; BIS, bioelectrical impedance spectroscopy; DXA, dual-energy X-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health Sarcopenia Project; GS, gait speed; HGS, handgrip strength; LBMI, lean body mass index; LTI, lean tissue index; MMI, muscle mass index; SD, standard deviation[79]; SM/BW, skeletal muscle/body weight; SMI, skeletal muscle mass index.

Publication bias and sensitivity analyses

No publication bias was detected in articles describing the prevalence of sarcopenia in patients on dialysis (Egger test: $P = 0.092$; Begg test: $P = 0.054$). Sensitivity analysis detected that the pooled prevalence of sarcopenia was not significantly affected by any individual study (*Figure* S9).

Discussion

This review describes the sarcopenia prevalence in patients on dialysis and how it was affected by the various definitions of sarcopenia. The varied prevalence of sarcopenia may partly be explained by the variability of the definitions. However, there were no statistical differences between the

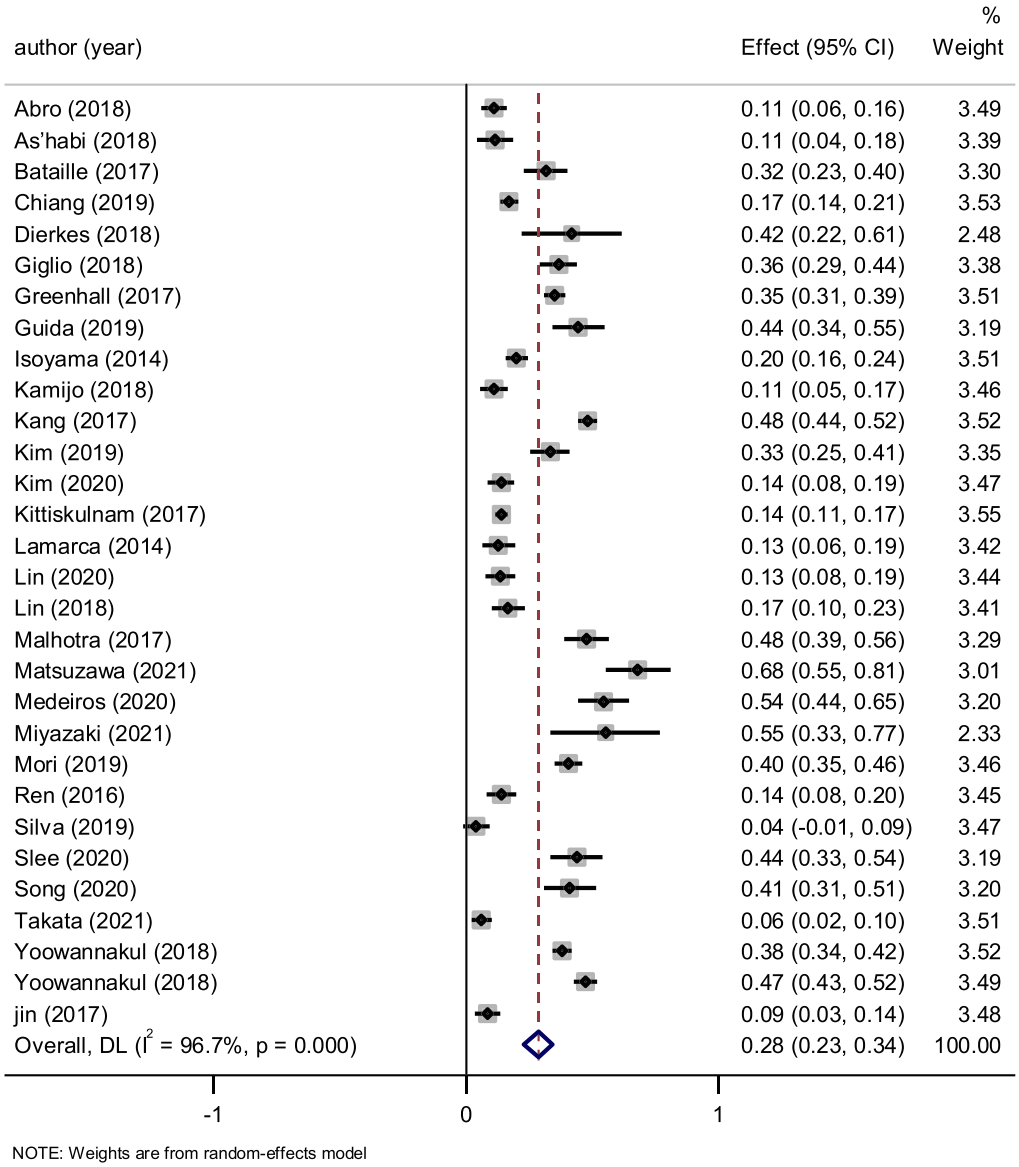

Figure 2 The pooled estimate prevalence of sarcopenia in dialysis patients.

different diagnostic items and different dialysis methods. Moreover, age and dialysis duration were not found to affect the prevalence of sarcopenia. Additionally, the pooled analyses indicated that combined criteria of sarcopenia (LMM plus LMS and/or LPP), LMM, and LMS in dialysis patients were all explicitly associated with an increased risk of mortality.

Because of exposure to long-term conditions of oxidation stress and metabolic dysregulation, together with loss of nutrients into the dialysate, protein-energy wasting (PEW)[50,51] presents universally in patients undergoing dialysis. Sarcopenia is both the main diagnostic criterion of PEW and an important manifestation of PEW, and its incidence is higher in dialysis patients. At present, the mechanism of sarcopenia in dialysis patients is not completely clear, but some mechanisms already explored include (i) chronic low-grade inflammation: firstly, kidney function deteriorates, then oxidative stress is activated, uraemic toxins accumulate, and abnormally high

Table 4 The impact of sarcopenia on mortality in dialysis patients

First author and year	Univariate HR (95% CI)	Multivariate HR (95% CI) without adjustment	Multivariate HR (95% CI) with adjustment	Adjustment factors	Follow-up time (months)[a]
Isoyama (2014)[23]			Combined criteria[b]: 1.93 (1.01–3.71) LMM: 1.23 (0.56–2.67) LMS: 1.98 (1.01–3.87)	Age, sex, diabetes, CVD, cholesterol, haemoglobin, GFR, and hs-CRP	29
Kamijo (2018)[28]			LMM: 1.9 (0.74–4.89) LMS: 0.95 (0.77–1.17)	Age, gender, walking speed, SMI, grip strength, and CFS	19.6
Kang (2017)[29]	LMM: 1.74 (1.35–2.24)	LMM: 1.71 (1.28–2.26)			48
Kittiskulnam (2017)[30]			Combined criteria[b]: 1.65 (0.88–3.08) LMM: 1.70 (0.94–3.05) LMS: 1.68 (1.01–2.79) LPP: 2.25 (1.36–3.74)	Age, sex, race, co-morbidities (diabetes mellitus, congestive heart failure, and coronary artery disease), and serum albumin	22.8
Malhotra (2017)[31]			LMM: 0.41 (0.15–1.1)	Age, gender, and sarcopenia obesity definitions	44
Giglio (2018)[35]		Combined criteria[b]: 2.02 (1.14–3.57) LMM: 1.49 (0.79–2.82) LMS: 2.03 (1.09–3.79)	Combined criteria[b]: 2.09 (1.05–4.20) LMM: 1.60 (0.73–3.53) LMS: 1.84 (0.92–3.68)	Age, gender, dialysis, vintage, and diabetes mellitus	36
Kim (2019)[40]			Combined criteria[b]: 6.99 (1.84–26.58) LMM: 2.77 (1.1–6.97) LMS: 5.65 (1.99–16.04)	Age, gender, BMI, *Kt/V*, albumin, diabetes, dialysis vintage, hs-CRP, and previous history of coronary artery disease and cerebrovascular disease	51.6
Mori (2019)[42]		Combined criteria[b]: 1.31 (0.81–2.1)			76
Kim (2020)[46]			LMM: 1.98 (0.6–6.48) LMS: 2.97 (0.91–7.1)	Age, gender, BMI, dialysis duration, diabetes, serum level of albumin, CAD, and PAOD	24
Song (2020)[47]			Combined criteria[b]: 2.72 (1.11–6.63)	Age, gender, BMI, diabetes, CAD, CVD, PAOD, and dialysis vintage	62.4

BMI, body mass index; CAD, coronary artery disease; CFS, Clinical Frailty Scale; CI, confidence interval; CVD, cerebrovascular disease; GFR, glomerular filtration rate; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; *Kt/V*, fractional clearance index for urea; LMM, lower muscle mass; LMS, lower muscle strength; LPP, lower physical performance; PAOD, peripheral artery occlusive disease; SMI, skeletal muscle index.
[a]Mean or median as reported.
[b]Combined criteria: LMM and either LMS or LPP.

levels of reactive oxygen species[52] and uraemic toxins stimulate the occurrence of inflammatory reactions.[53] Secondly, the decline of renal function results in a reduced capacity to excrete inflammatory factors, which leads to the persistence of the inflammatory response[3]; therefore, inflammatory cytokines, for example, tumour necrosis factor-α, and interleukin-6 and interleukin-1, are often significantly increased in patients with ESRD,[54–56] which increases the degradation and decreases the synthesis of muscle protein, resulting in muscle atrophy.[57] (ii) Changes in hormone levels: an imbalance of hormone levels, presenting as decreasing levels of growth hormone, sex hormones (especially testosterone), insulin, and insulin-like growth factor-1,[58] and increasing parathyroid hormone,[59] glucocorticoids, and angiotensin II,[60] and their interaction with the corresponding hormone receptor cause decreased protein synthesis and increased protein decomposition, eventually leading to the emergence of sarcopenia.[2,5] (iii) Changes in living status: reductions in appetite due to metabolic waste accumulation and some prescribed drugs, the imbalance of appetite-regulating hormones, dietary restrictions, and gastrointestinal fullness may all lead to insufficient protein intake.[61] Meanwhile, restricted activity during and fatigue after dialysis shortens the time taken for physical activity, which impairs muscle function. (iv) Protein loss during

DOI: 10.1002/jcsm.12890

dialysis: both HD and PD procedures stimulate protein degradation and reduce protein synthesis, and these responses persist following dialysis,[4,5] also leading to loss of muscle mass. Of note, the mechanism of sarcopenia in dialysis patients is complicated and remains an aspect of research that merits consideration in the future.

Sarcopenia definitions used in diagnosing dialysis patients include LMM alone or combined criteria (LMM plus LMS and/or LPP), such as EWGSOP criteria, AWGS criteria, Foundation for the National Institutes of Health criteria, and International Working Group on Sarcopenia criteria. When only LMM was assessed, the pooled prevalence was estimated at 34.6%, while assessed combined criteria (LMM plus LMS and/or LPP) lowered it to 25.9%. The prevalence of sarcopenia presented an increasing trend in studies that used LMM alone, although the difference was not statistically significant. However, this merged result was lacking robustness caused by the high heterogeneity and small sample size of some studies among the included literature. For example, in two included articles that both diagnosed sarcopenia by combined criteria (LMM plus LMS and/or LPP), one reported the prevalence of sarcopenia in dialysis as 4%,[13] while the value in the other was 68%,[14] and both only involved 50 cases. The random-effects model was applied in response to the high heterogeneity between the studies; however, the differences between the two groups became statistically significant when we implemented the fixed-effects model, and this further proved that the merged result was not satisfactorily robust and the conclusion lacked reliability. At the same time, there was no statistical evidence of a difference between PD and HD populations, but sarcopenia seemed to be more prevalent in HD patients than PD patients. The present studies show that, compared with HD, PD has some advantages in preserving muscle mass and muscle function. Firstly, younger patients with ESRD who are in better physical condition are more likely to choose PD, as they are likely to have muscles of a better status. Secondly, compared with HD patients, PD-treated patients have well-preserved residual renal function and fewer complications.[62] Additionally, PD is associated with better cognitive function[63] and life quality[62] than HD. All of these advantages of PD result in the conservation of muscle mass and muscle function.

Although sarcopenia has been traditionally seen as a condition associated with age, controversially, the age of the patients failed to demonstrate any clear influence on sarcopenia prevalence in our systematic review, implicating the importance of screening sarcopenia even in young dialysis patients. Of course, this relationship requires verification in studies with large dialysis cohorts. Moreover, the regression analysis suggested that the duration of dialysis had no significant effect on the incidence of sarcopenia. This result might relate to the fact that most of the included studies were interested in patients during the maintaining dialysis stage, whose physical condition tends to be relatively steady. As shown in the studies, physical function was in obvious decline for 3 months and mortality rates were consistently higher in the first 4 months after starting dialysis. However, the physical condition of dialysis patients is relatively steady in the maintaining dialysis stage, in which prolonged dialysis times may not have a significant effect on their physical condition.[64,65]

In the general population, obesity is linked to a higher risk of cardiovascular disease and mortality. However, some studies found that elevated body mass index (BMI) was associated with improved survival in dialysis patients, which was described as the 'obesity paradox'.[66–68] The reason for this contradiction may lie in the decrease in BMI in dialysis patients that signifies the development or progression of sarcopenia, PEW, and cachexia, which have a clear association with poor prognoses in dialysis patients. The pooled analyses of 10 studies showed that the combined criteria of sarcopenia (LMM plus LMS and/or LPP) as well as LMM alone and LMS alone are strong mortality predictors. Compared with LMM, LMS was more robustly associated with mortality. Underpinning this, LMS is considered a component of severe sarcopenia. Because only one of the 10 studies measured LPP, we could not apply a meta-analysis. However, this study indicated that the risk of death in dialysis patients with LPP is significantly increased. Therefore, for some settings in which it is difficult to measure multiple items of sarcopenia, such as ICUs, one or two of the items can have prognostic value.

To our best knowledge, this systematic review is the first to compare the diagnostic methods and prevalence of sarcopenia in dialysis patients. The study provides an up-to-date and accurate estimation of sarcopenia prevalence among the dialysis population, which is necessary in the calculation of sample size for future intervention studies in this arena. Additionally, in the randomized placebo-controlled trials, the prevalence of the placebo group can compare with this meta-analysis to ensure the placebo group has the expected prevalence. Meanwhile, understanding baseline patient characteristics that increase sarcopenia is critical for balanced randomization in interventional trials to prevent sarcopenia. Although the subgroup analysis did not find statistically significant population characteristics that increased the risk of sarcopenia, it was found that HD had a higher tendency to suffer from sarcopenia than PD. Moreover, it was found that sarcopenia was consistently associated with mortality in dialysis patients, which reinforces that the widespread and early clinical implementation of sarcopenia screening should help identify those at an increased risk of future health issues and help direct preventive therapies. For dialysis patients with sarcopenia, we should not only treat their medical disorders but also intervene in the progression of their sarcopenia to improve their prognoses and reduce their family and social healthcare burdens.

As with most studies, the design of this review was not without some limitations. Firstly, we only included literature

released in English publications, which might have lent a selective bias to this review. Secondly, there was significant heterogeneity between the included studies in terms of the diagnostic methods, measurement approaches, and diagnostic thresholds, and so forth. Secondly, most of the included studies were cross-sectional and had small cohorts, which can also lead to some between-study heterogeneity. It is crucial, therefore, that future studies employ not only standardized methods of sarcopenia diagnosis but also adequate sample sizes to improve the quality of the original research. Thirdly, despite extracting adjusted estimates for multivariate analyses from the contributing studies, residual bias and confounding remain a possibility. Finally, although this review included studies from different continents (Asia, Europe, North America, and South America), data from Africa were not available, which limits its worldwide applicability.

Conclusions

Sarcopenia is an important clinical condition shown to be prevalent in a clinically significant proportion of dialysis patients that is associated with a higher mortality risk. However, the clinical heterogeneity caused by the different diagnostic criteria, assessment procedures, and diagnostic thresholds for sarcopenia is substantial. Effective diagnostic criteria are key to the expeditious identification of sarcopenia in patients, and future longitudinal studies are needed to optimize management strategies aiming to improve individuals' lives and reduce family and social healthcare burdens.

Author contributions

X.S. and J.Y. were involved in the study design, study protocol development, all analyses, and the management of all aspects of the systematic review. All co-authors were involved in the literature search and participated in screening, full-text reviewing, and data extracting. J.Y. provided advice on the analyses and aided in their interpretation. X.S. contributed to the writing of the final manuscript, and all co-authors approved the final version for submission.

Acknowledgement

We thank Dr Chenkai Wu for providing editorial assistance to the manuscript.

Conflict of interest

None declared.

Funding

This study was supported by grants from Chinese National Science & Technology Pillar Program (2020YFC2005600/02); Sichuan Province Science and Technology Support Program (2019YFS0277 and 2021YFS0136); 1·3·5 Project for Disciplines of Excellence—Clinical Research Incubation Project, West China Hospital, Sichuan University (19HXFH012); 1·3·5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (ZYJC21005); and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (Z20191003 and Z2018B13).

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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