


# Diagnosis, prevalence, and outcomes of sarcopenia in kidney transplantation recipients: A systematic review and meta-analysis

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## Abstract

The prevalence of sarcopenia and its clinical predictors and clinical impact vary among kidney transplant recipients (KTRs), in part because of different diagnostic criteria. This study aimed to assess the reported diagnosis criteria of sarcopenia and compare them in terms of prevalence, clinical predictors, and impact of sarcopenia. The Medline, Embase, and Cochrane Library were searched for the full-length reports published until 28 January 2022. The subgroup analysis, meta-regression, and sensitivity analysis were performed and heterogeneity was assessed using the  $I^2$ . A total of 681 studies were retrieved, among which only 23 studies (including 2535 subjects, 59.7% men, mean age 49.8 years) were eventually included in the final analysis. The pooled prevalence in these included studies was 26% [95% confidence interval (95% CI): 20–34%,  $I^2 = 93.45\%$ ], including 22% (95% CI: 14–32%,  $I^2 = 88.76\%$ ) in men and 27% (95% CI: 14–41%,  $I^2 = 90.56\%$ ) in women ( $P = 0.554$  between subgroups). The prevalence of sarcopenia diagnosed using low muscle mass was 34% (95% CI: 21–48%,  $I^2 = 95.28\%$ ), and the prevalence of using low muscle mass in combination with low muscle strength and/or low physical performance was 21% (95% CI: 15–28%,  $I^2 = 90.37\%$ ) ( $P = 0.08$  between subgroups). In meta-regression analyses, the mean age (regression coefficient: 1.001, 95% CI: 0.991–1.011) and percentage male (regression coefficient: 0.846, 95% CI: 0.367–1.950) could not predict the effect size. Lower body mass index (odds ratio (OR): 0.57, 95% CI: 0.39–0.84,  $I^2 = 61.5\%$ ), female sex (OR: 0.31, 95% CI: 0.16–0.61,  $I^2 = 0.0\%$ ), and higher age (OR: 1.08, 95% CI: 1.05–1.10,  $I^2 = 10.1\%$ ) were significantly associated with a higher risk for sarcopenia in KTRs, but phase angle (OR: 0.81, 95% CI: 0.16–4.26,  $I^2 = 84.5\%$ ) was not associated with sarcopenia in KTRs. Sarcopenia was not associated with rejections (risk ratio (RR): 0.67, 95% CI: 0.23–1.92,  $I^2 = 12.1\%$ ), infections (RR: 1.03, 95% CI: 0.34–3.12,  $I^2 = 87.4\%$ ), delayed graft functions (RR: 0.81, 95% CI: 0.46–1.43,  $I^2 = 0.0\%$ ), and death (RR: 0.95, 95% CI: 0.32–2.82,  $I^2 = 0.0\%$ ) in KTRs. Sarcopenia was found to be very common in KTRs. However, we have not found that sarcopenia had a negative impact on clinical health after kidney transplantation. Large study cohorts and multicentre longitudinal studies in the future are urgently needed to explore the prevalence and prognosis of sarcopenia in kidney transplant patients.

**Keywords** Diagnosis; Prevalence; Sarcopenia; Kidney transplantation

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## Introduction

Kidney transplantation (KT) improves survival and quality of life in end-stage kidney disease (ESKD) patients and is less expensive than numerous rounds of dialysis, thus making KT a preferred form of renal replacement therapy.<sup>1</sup> The 2020 Kidney Disease: Improving Global Outcomes Clinical Practice Guideline recommends that all patients with chronic kidney disease (CKD) stages G4-G5 who are expected to progress to ESRD should be informed of considering for KT.<sup>2</sup> A recent study found that the prevalence of sarcopenia in CKD patients ranges from 4% to 42%.<sup>3</sup> Another meta-analysis found a 28.5% prevalence of sarcopenia in CKD patients with dialysis.<sup>4</sup> Harada *et al.* suggested that a theoretically successful KT could improve metabolic disorder, activity, and appetite in CKD patients and restore body composition to a healthy state. However, they found that successful KT changed only part of the body composition and, interestingly, decreased muscle mass.<sup>5</sup> Some studies have reported that after KT the prevalence of sarcopenia in KT recipients (KTRs) ranges from 3.7% to 72.1%, and some studies have found that the prevalence of sarcopenia is increased compared with that before KT.<sup>6–8</sup> The current study identified some causes of sarcopenia in CKD patients, such as increased inflammation, oxidative stress, and uraemic toxins (due to anorexia, acidosis, and anaemia) that can lead to impaired protein assimilation and increased muscle atrophy.<sup>9,10</sup> The shock of KT, decreased postoperative activity, and immunosuppressive drugs, including corticosteroids, specific metabolic abnormalities associated with calcineurin inhibitors may contribute to the development of sarcopenia after KT, which may partially explain the findings in some studies that the prevalence of sarcopenia after KT is higher than that before KT.<sup>11–13</sup> It has been shown that muscle mass is inversely related to mortality and graft loss in KTRs, and patients having a higher muscle mass might have better survival outcomes after KT.<sup>14,15</sup> Therefore, it is important to assess muscle mass during the screening for eligibility for receiving KT.

In current studies on sarcopenia in KTRs, there is a huge difference in the rate of prevalence of sarcopenia, which is reportedly between 3.7%<sup>7</sup> and 72.1%,<sup>6</sup> possibly due to the inclusion of different diagnostic criteria and/or sample sizes. Common diagnostic criteria of sarcopenia in KTRs follow the European Working Group on Sarcopenia in Older People (EWGSOP)<sup>16,17</sup> and the Asian Working Group for Sarcopenia (AWGS).<sup>18,19</sup> However, the clinical predictors of sarcopenia and its impacts on outcomes in KTRs remain unclear. Thus, this review aimed to evaluate the studies of literature on KTRs to identify the most commonly practiced diagnostic criteria of sarcopenia, its prevalence, clinical predictors, and outcomes.

## Methodology

This study was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was registered in PROSPERO (ID: CRD42022315040).<sup>20</sup>

### Search strategy

The Medline, Embase, and Cochrane Library were searched via Ovid SP until 28 January 2022, using the strategy as described in *Table S1*. Manual searching for the reference lists of eligible studies was performed. There was no language restriction.

### Inclusion and exclusion criteria

All studies reporting sarcopenia in all ages with all types of KTRs were included, and the diagnosis of sarcopenia was defined according to the criteria provided in the article's methodology. The criteria for exclusion of studies were as follows: (i) no data on diagnosis and prevalence of sarcopenia; (ii) reviews, comments, conference abstracts, editorials, notes, letters, consensus and guidelines, and case reports or animal studies; and (iii) duplicate studies.

### Outcomes

The major outcomes of the study were (i) identification of frequently applied diagnostic criteria and prevalence rate of sarcopenia; (ii) determination of clinical predictors of sarcopenia; and (iii) comparative analysis between KTRs with or without sarcopenia, concerning (a) quality of life, from all types of questionnaires; (b) physical activity level; (c) kidney transplantation records, for example, complications, infections, hospital readmission, rejection and delayed graft function; (d) inflammation biomarkers, for example, white cell count and C-reactive protein (CRP) level, and (e) all-cause mortality.

### Study selection

Two authors (J. Z. and M. Z.) independently screened all articles by their titles and abstract contents after duplicate removal and then separately assessed only the full-text articles following the inclusion and exclusion criteria. A third author (H. G.) examined and made the final decision on the studies included.

## Data extraction and quality assessment

A preformatted sheet was used to extract data from eligible studies by two authors (J. Z. and Q. Z.) independently, and a third author (H. G.) reviewed and finalized the data. Extracted data included the following information: first author name, region, year, study design method, sex, sample size, age, male (%), the diagnostic criteria and prevalence rate of sarcopenia, kidney transplantation data, the clinical predictors of sarcopenia, and outcomes.

The methodological quality of the cross-sectional and case-control/cohort studies was evaluated based on the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.<sup>21</sup> And a tool was used to assess the risk of bias in prevalence studies.<sup>22</sup> Each study was evaluated independently by two authors, and any disagreement was resolved by discussion with a third reviewer.

## Statistical analyses

A meta-analysis was used to calculate the weight of prevalence, the clinical predictors, and outcomes of sarcopenia in KTRs. Among studies evaluating sarcopenia following different diagnostic criteria, we aggregated those prevalence closest to the EWGSOP-2019 recommendations.<sup>17</sup> For studies reporting the prevalence of sarcopenia in both men and women, we summarized the prevalence by sex. We extracted the odds ratios (ORs) and 95% confidence intervals (95% CIs) of the predictors of sarcopenia from multivariate analyses for meta-analysis. All values were reported as point estimates with 95% CI in parentheses. Dichotomous variables were tested using both risk ratios (RRs) and ORs. Continuous variables were tested using both mean difference (MD) and standard mean difference (SMD). A  $P < 0.05$  was considered statistically significant.

Heterogeneity was assessed using the  $I^2$  values of 25%, 50%, and 75% were indicated to be low, moderate, and high levels of heterogeneity, respectively.<sup>23</sup> A fixed-effects model (Mantel-Haenszel method) was used when there was no heterogeneity among the studies.<sup>24</sup> A random-effects model (DerSimonian and Laird method) was used if heterogeneity existed.<sup>25</sup>

Subgroup analysis was performed according to definitions (1 vs. >1 diagnostic criteria) of sarcopenia (EWGSOP, AWGS, and others), evaluated via chi-square ( $\chi^2$ ) test, and then meta-regression was performed including the average age and sex (percentage male). We conducted a sensitivity analysis test to assess the robustness of summary estimates by excluding unfit studies one by one. Egger bias test<sup>26</sup> and Begg-Mazumdar Kendall's tau<sup>27</sup> were used to evaluate the publication bias. We used the trim-and-fill approach if there

was any publication bias.<sup>28</sup> The meta-analysis was performed with STATA 12.0 (StataCorp, College Station, TX, USA).

## Results

Figure 1 shows the details of the literature selection. A total of 681 studies were retrieved, among which 43 studies were found with the full text. Out of these, 20 studies were excluded for reasons detailed in Table S2. Finally, 23<sup>6–8,29–48</sup> studies were included, involving 2535 KTRs with 59.7% of male subjects. Of these, nine studies were from Europe, seven were from Asia, five were from South America, one was from North America, and one was from Oceania. The characteristics of the included studies are shown in Table 1. The included studies were observational, including 13 cross-sectional design, 7 prospective studies, and 3 reported retrospective data. The overall quality of included studies was moderate (Table S3). Among the included studies, 8 studies were with a moderate risk of bias, and 15 studies had a low risk of bias in the assessment of the risk of bias in prevalence (Table S4).

## Diagnosis of sarcopenia

The diagnostic criteria used to assess sarcopenia are summarized in Table 1. Ten studies<sup>6,8,29–31,34–37,48</sup> used low muscle mass (LMM) as the sole diagnostic criterion, whereas 13 studies<sup>7,32,33,38–47</sup> used LMM in combination with low muscle strength (LMS) and/or low physical performance (LPP). The different cut-off thresholds used to define sarcopenia for each of the included studies are listed in Table 2.<sup>49–57</sup> LMM was measured via dual-energy X-ray absorptiometry (six studies),<sup>7,31,34,39,42,45</sup> bioelectrical impedance analysis (10 studies),<sup>8,32,33,38,40,41,43,44,46,47</sup> and computed tomography (CT, six studies).<sup>6,29,30,35–37</sup> LMS was measured by HGS (14 studies).<sup>7,33,38–48</sup> LPP was measured by GS, including 4mGS (four studies),<sup>33,40,42,43</sup> 6mGS (two studies),<sup>32,39</sup> and 10mGS (two studies).<sup>41,45</sup> The EWGSOP<sup>16,17</sup> (14 studies)<sup>7,32–34,38–40,42–44,46–48</sup> and AWGS<sup>18,19</sup> (4 studies)<sup>31,32,41,45</sup> recommended thresholds were common. A comparison of the main guidelines used to detect sarcopenia in KTRs is shown in Table S5.

## Sarcopenia prevalence

The pooled prevalence in the included studies was 26% (95% CI: 20–34%,  $I^2 = 93.45\%$ ,  $P < 0.001$ ; Figure 2). Eleven studies and 11 studies provided data on the prevalence of sarcopenia in males and females, respectively, and the pooled prevalence was 22% (95% CI: 14–32%,  $I^2 = 88.76\%$ ,  $P < 0.001$ ) and 27% (95% CI: 14–41%,  $I^2 = 90.56\%$ ,  $P < 0.001$ ),

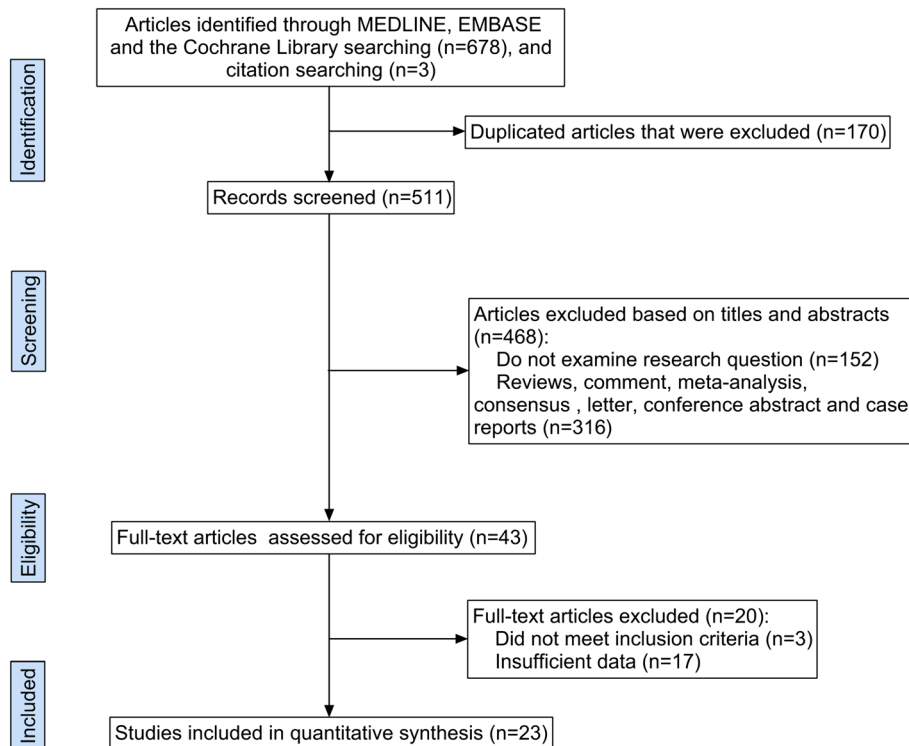


Figure 1 Flow diagram of study selection process.

respectively. The difference was not statistically significant ( $P = 0.554$ ) (Figure S1).

### Subgroup analysis, meta-regression, and sensitivity analysis

The prevalence of sarcopenia diagnosed using LMM was 34% (95% CI: 21–48%,  $I^2 = 95.28\%$ ,  $P < 0.001$ ), which was higher than that of the combination of LMM and LMS and/or LPP (21%, 95% CI: 15–28%,  $I^2 = 90.37\%$ ,  $P < 0.001$ ). But the difference was not statistically significant ( $P = 0.08$ , Figure S2). Rates of sarcopenia defined by AWGS, EWGSOP, and other methods were 21% (95% CI: 9–36%,  $I^2 = 89.44\%$ ,  $P < 0.001$ ), 23% (95% CI: 17–30%,  $I^2 = 89.28\%$ ,  $P < 0.001$ ), and 36% (95% CI: 15–59%,  $I^2 = 97.10\%$ ,  $P < 0.001$ ), respectively. However, there were no statistically significant differences ( $P = 0.526$ , Figure S3). In meta-regression analyses, the mean age (regression coefficient: 1.001, 95% CI: 0.991–1.011,  $P = 0.775$ ) and the percentage of male subjects (regression coefficient: 0.846, 95% CI: 0.367–1.950,  $P = 0.681$ ) could not predict the effect size (Figures S4 and S5). Sensitivity analysis showed that omitting any of the included studies did not significantly affect the risk of bias in the prevalence of sarcopenia (Figure S6).

### Clinical predictors of sarcopenia

Thirteen studies provided data on the clinical predictors of sarcopenia in KTRs. Higher body mass index (BMI) (OR: 0.82, 95% CI: 0.68–0.99,  $I^2 = 61.5\%$ ,  $P < 0.001$ , three studies), male gender (OR: 0.31, 95% CI: 0.16–0.61,  $I^2 = 0.0\%$ ,  $P = 0.584$ , two studies) was significantly associated with a lower risk for sarcopenia in KTRs, whereas age (OR: 1.08, 95% CI: 1.05–1.10,  $I^2 = 10.1\%$ ,  $P = 0.329$ , three studies) was significantly associated with a higher risk. Phase angle (OR: 0.81, 95% CI: 0.16–4.26,  $I^2 = 84.5\%$ ,  $P = 0.011$ , two studies) was not significantly associated with risk for sarcopenia in KTRs (Figure 3). Due to the lack of sufficient data to perform a quantitative meta-analysis, the results of the remaining review of clinical predictors of sarcopenia are summarized in Table S6. Additionally, the results of a review of clinical predictors of HGS are summarized in Table S7.

### Clinical outcomes of sarcopenia

Studies that reported the clinical outcomes in median and interquartile ranges (IQR) were included in Table 3. KTRs with sarcopenia had the worse quality of life (measured by SF-26)<sup>44</sup> and lower physical activity levels.<sup>42,44</sup> Sarcopenia was not associated with rejections (RR: 0.67, 95% CI: 0.23–1.92,

Table 1 Studies included characteristics

Study, year, country	Study design	Male (%)	Sample size	Age [mean $\pm$ SD or median (IQR)]	Living donor (%)	Dialysis time (month)	Diagnostic criteria of sarcopenia	Criteria (assessment method to detect sarcopenia)	Prevalence of sarcopenia		
									Female (%)	Male (%)	Total (%)
Wong et al. 2022 <sup>29</sup> Australia	Retrospective	71.4	63	57 (48.5–63.5)	71.4	-	Others*	LMM (CT)	77.8	44.4	54.0
Morel et al. 2021 <sup>30</sup> France	Retrospective cohort	61.5	200	54.8 $\pm$ 13.8	13.0	2.2	Others*	LMM (CT)	3.9	5.7	5.0
Mazzola et al. 2021 <sup>6</sup> France	Prospective cohort	25.8	31	58 (53–63)	-	-	Others*	LMM (CT)	89.5	58.3	72.1
Koito et al. 2021 <sup>31</sup> Japan	Cross-sectional	72.5	40	52.1 $\pm$ 11.7	-	21.6	AWGS (2019)	LMM (DXA)	51.7	45.5	50.0
Khoo et al. 2021 <sup>32</sup> Taiwan	Cross-sectional	48.4	95	45.2 $\pm$ 10.9	-	-	AWGS (2019) EWGSOP (2019)	LMM (BIA) LMS (HGS) LPP (6mGS)	10.2	13.0	11.6
dos Reis et al. 2021 <sup>33</sup> Brazil	Cross-sectional	68.0	125	48 $\pm$ 12	39.1	48	EWGSOP (2019)	LMM (BIA) LMS (HGS) LPP (4mGS) LMM (DXA)	10.0	22.4	18.4
Dienemann et al. 2021 <sup>34</sup> Germany	Prospective cohort	51.7	60	46 (20–60)	45.0	28.8	Others*	-	-	-	11.7
Deliege et al. 2021 <sup>35</sup> France	Retrospective	58.2	122	66 $\pm$ 4.3	5.7	30.9	EWGSOP (2019)	LMM (CT)	29.4	22.5	25.4
Chen Y., et al. 2021 <sup>36</sup> China	Prospective	55.0	40	25 (17–39)	-	-	Others*	LMM (CT)	-	-	47.5
Chen X., et al. 2021 <sup>37</sup> Maryland	Prospective cohort	59.3	275	55.5 $\pm$ 12.5	-	-	Others*	LMM (CT)	-	-	39.6
Woloznyk et al. 2020 <sup>38</sup> Poland	Prospective cohort	58.9	95	50.8 $\pm$ 13.4	-	-	EWGSOP (2010 or 2019)	LMM (BIA) LMS (HGS)	-	-	31.6
Nanmoku et al. 2020 <sup>8</sup> Japan	Prospective	62.5	80	44.6 $\pm$ 13.2	-	20.5	EWGSOP (2010)	LMM (BIA)	-	-	38.8
Martins et al. 2020 <sup>39</sup> Brazil	Cross-sectional	57.8	83	48.8 $\pm$ 12.1	45.8	-	EWGSOP (2010)	LMM (DXA) LMS (HGS) LPP (6mGS)	-	-	19.3
Limiro et al. 2020 <sup>40</sup> Brazil	Cross-sectional	68.5	127	47.6 $\pm$ 11.5	-	55.4	EWGSOP (2019)	LMM (BIA) LMS (HGS) LPP (4mGS)	-	-	18.9
Kosoku et al. 2020 <sup>41</sup> Japan	Cross-sectional	58.1	210	55 (45–66)	82.9	45	AWGS (2014)	LMM (BIA) LMS (HGS) LPP (10mGS)	18.2	6.6	11.4
Bellafronte et al. 2020 <sup>7</sup> Spain	Cross-sectional	59.3	81	49 $\pm$ 8	-	79	EWGSOP (2019)	LMM (DXA) LMS (HGS)	-	-	3.7
Menna Barreto et al. 2019 <sup>42</sup> Brazil	Cross-sectional	57.3	185	50 (18–65)	-	36	EWGSOP (2019)	LMM (DXA) LMS (HGS) LPP (4mGS)	11.4	11.3	11.4
Dos Reis et al. 2019 <sup>43</sup> Brazil	Cross-sectional	68.2	129	47.8 $\pm$ 11.8	37.2	-	EWGSOP (2010)	LMM (BIA) LMS (HGS) LPP (4mGS)	-	-	49.6
Chan et al. 2019 <sup>44</sup> United Kingdom	Prospective	56.3	128	49 $\pm$ 15	-	24	EWGSOP (2010)	LMM (BIA) LMS (HGS)	-	-	28.9
Yanishi et al. 2018 <sup>45</sup> Japan	Cross-sectional	72.4	58	46.6 $\pm$ 12.7	-	33.6	AWGS (2014)	LMM (DXA) LMS (HGS) LPP (10mGS)	25.0	19.0	20.7
Malgorzewicz et al. 2018 <sup>46</sup> Poland	Cross-sectional	52.9	70	49.89 $\pm$ 13.4	-	-	EWGSOP (2010 or 2019)	LMM (BIA) LMS (HGS)	-	-	33.3
Dierkes et al. 2018 <sup>47</sup> Norway	Cross-sectional	70.8	72	60 (49, 67)	-	-	EWGSOP (2010)	LMM (BIA) LMS (HGS)	-	-	31.9
Ozkayir et al. 2014 <sup>48</sup> Turkey	Cross-sectional	59.0	166	37.9 $\pm$ 11.9	-	-	EWGSOP (2010)	LMS (HGS)	22.4	17.6	20.5

Abbreviations: AWGS, Asian Working Group for Sarcopenia; BIA, bioelectrical impedance analysis; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older People; GS, gait speed; HGS, handgrip strength; IQR, interquartile range; KT, kidney transplant; LMM, lower muscle mass; LMS, lower muscle strength; LPP, lower physical performance; SD, standard deviation.

\*Diagnostic criteria of sarcopenia other than EWGSOP (2010 or 2019) and AWGS (2014 or 2019).

**Table 2** Criteria and cut-off points used to detect sarcopenia in included studies

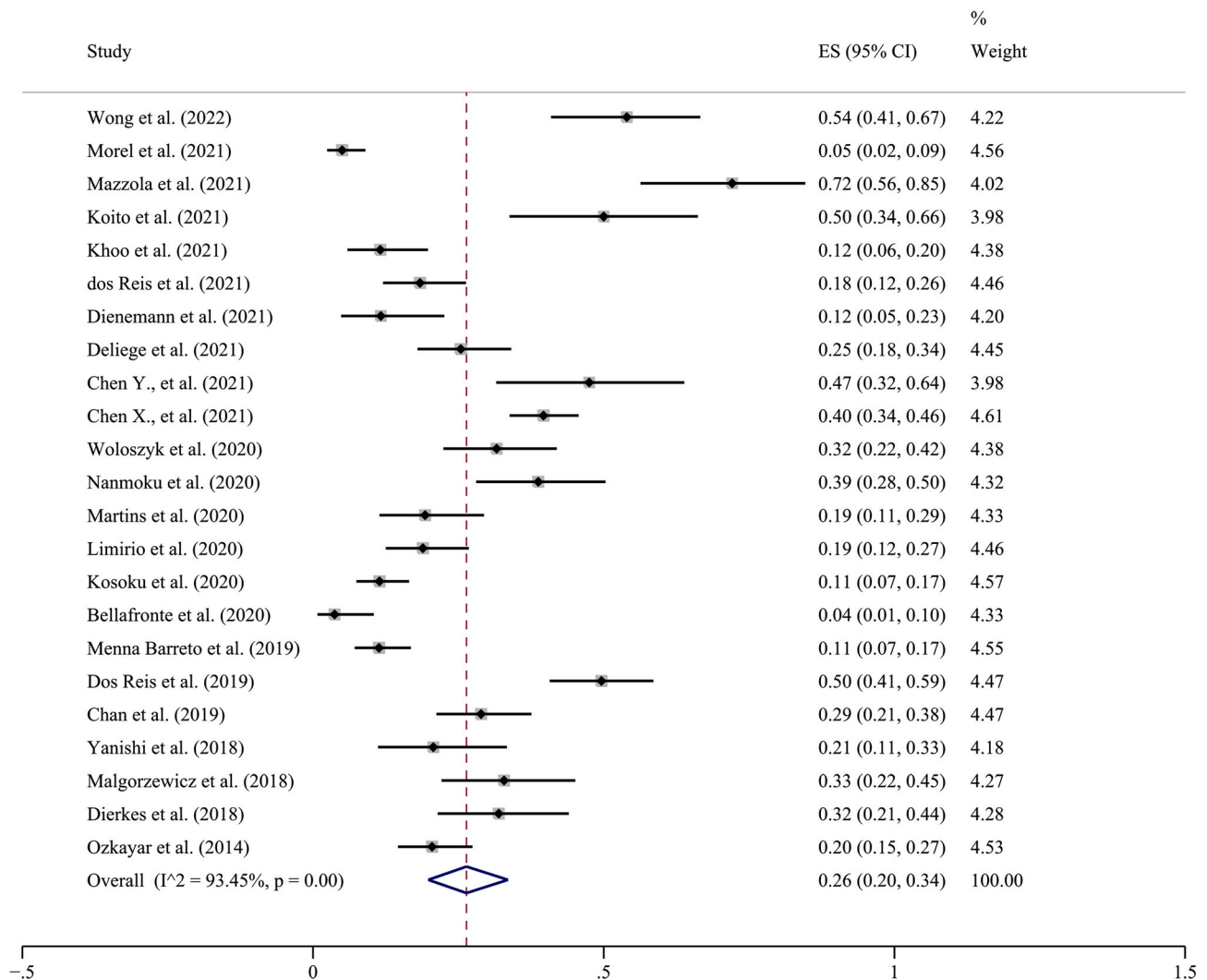
Criteria	References	
<b>Lower muscle mass</b>		
DXA	1. EWGSOP (2010) ASMI: <7.26 kg/m <sup>2</sup> for men and <5.5 kg/m <sup>2</sup> for women. 2. EWGSOP (2019) ALM: <20 kg for men and <15 kg for women. 3. EWGSOP (2019) SMI/height <sup>2</sup> : <7.26 kg/m <sup>2</sup> for men and <5.5 kg/m <sup>2</sup> for women. 4. AWGS (2014) SMI: <7.0 kg/m <sup>2</sup> for men and <5.4 kg/m <sup>2</sup> for women. 5. AWGS (2019) SMI: <7.0 kg/m <sup>2</sup> for men and <5.4 kg/m <sup>2</sup> for women. 6. Batsis et al. (2013) <sup>43</sup> ALMI: <2 SD below young adult mean.	Martins et al. 2020 <sup>39</sup> Bellafronte et al. 2020 <sup>7</sup> Menna Barreto et al. 2019 <sup>42</sup> Yanishi et al. 2018 <sup>45</sup> Koito et al. 2021 <sup>31</sup> Dienemann et al. 2021 <sup>34</sup> Chan et al. 2019 <sup>44</sup>
BIA	1. EWGSOP (2010) Wieskotten et al. LTI < gender- and age- specific cutoffs from a reference. 2. EWGSOP (2010) SMI: <8.87 kg/m <sup>2</sup> for men and <6.42 kg/m <sup>2</sup> for women. 3. EWGSOP (2010) Janssen et al. 2002 MMI: <10.76 kg/m <sup>2</sup> for men and <6.76 kg/m <sup>2</sup> for women. 4. EWGSOP (2019) ASMI: <7.0 kg/m <sup>2</sup> for men and <5.5 kg/m <sup>2</sup> for women.  5. EWGSOP (2010 or 2019) Beaudart et al. (2018) <sup>44</sup> LTI: <14 kg/m <sup>2</sup> for both genders. 6. AWGS (2014) SMI: <7.0 kg/m <sup>2</sup> for men and 5.7 kg/m <sup>2</sup> for women.  7. Jin et al. (2019) <sup>45</sup> SMI: <16.5 kg/m <sup>2</sup> in men and <14.2 kg/m <sup>2</sup> in women.	Dierkes et al. 2018 <sup>47</sup> Dos Reis et al. 2019 <sup>43</sup>  dos Reis et al. 2021 <sup>33</sup> and Limirio et al. 2020 <sup>40</sup> Woloszyk et al. 2020 <sup>38</sup> and Malgorzewicz et al. 2018 <sup>46</sup> Nanmoku et al. 2020 <sup>8</sup> and Kosoku et al. 2020 <sup>41</sup> Khoo et al. 2021 <sup>32</sup>
CT	1. Thoresen et al. (2012) <sup>46</sup> the total psoas area below 1561 mm <sup>2</sup> in men and 1464 mm <sup>2</sup> in women. 2. Shachar et al. (2016) <sup>47</sup> SMI: <55.4 kg/m <sup>2</sup> in men and <41.0 kg/m <sup>2</sup> in women. 3. Montgomery et al. (2019) <sup>48</sup> SMI: <50 kg/m <sup>2</sup> in men and <39 kg/m <sup>2</sup> in women. 4. Derstine et al. (2018) <sup>49</sup> SMI: <44.6 kg/m <sup>2</sup> in men and <34.0 kg/m <sup>2</sup> in women. 5. Martin et al. (2018) <sup>50</sup> SMI: <41 cm <sup>2</sup> /m <sup>2</sup> in women, <43 cm <sup>2</sup> /m <sup>2</sup> in men with a BMI < 25 kg/m <sup>2</sup> and < 53 cm <sup>2</sup> /m <sup>2</sup> in men with a BMI > 25 kg/m <sup>2</sup> . 6. SMI: < the lower limit of the prediction interval for 95% of healthy subjects.	Mazzola et al. 2021 <sup>6</sup>  Chen, Y. et al. 2021 <sup>36</sup> Chen, X. et al. 2021 <sup>37</sup> Deliege et al. 2021 <sup>35</sup> Wong et al. 2022 <sup>29</sup>  Morel et al. 2021 <sup>30</sup>
<b>Lower muscle strength</b>		
HGS	1. EWGSOP (2010) Laurentani et al. (2003) <sup>51</sup> HGS: <30 kg for men and <20 kg for women.  2. EWGSOP (2019) HGS: <27 kg for men and <16 kg for women.  3. AWGS (2019) HGS: <28 kg for men and <18 kg for women. 4. EWGSOP (2010 or 2019) Beaudart et al. (2018) <sup>44</sup> HGS: <46 kg for men and <26 kg for women. 5. AWGS (2014) HGS: <26 kg for men and <18 kg for women.	Martins et al. 2020, <sup>39</sup> Dos Reis et al. 2019, <sup>43</sup> Chan et al. 2019, <sup>44</sup> Dierkes et al. 2018 <sup>47</sup> and Ozkayar et al. 2014 <sup>48</sup> dos Reis et al. 2021, <sup>33</sup> Limirio et al. 2020, <sup>40</sup> Bellafronte et al. 2020 <sup>7</sup> and Menna Barreto et al. 2019 <sup>42</sup> Khoo et al. 2021 <sup>32</sup> Woloszyk et al. 2020 <sup>38</sup> and Malgorzewicz et al. 2018 <sup>46</sup> Kosoku et al. 2020 <sup>41</sup> and Yanishi et al. 2018 <sup>45</sup>
<b>Lower physical performance</b>		
4mGS	1. EWGSOP (2019) GS: <0.8 m/s (both genders).	dos Reis et al. 2021, <sup>33</sup> Limirio et al. 2020, <sup>40</sup> and Menna Barreto et al. 2019 <sup>42</sup>
6mGS	2. EWGSOP (2010) GS: <0.8 m/s (both genders). 1. AWGS (2019) GS: <1.0 m/s (both genders). 2. EWGSOP (2010) GS: <0.8 m/s (both genders).	Dos Reis et al. 2019 <sup>43</sup> Khoo et al. 2021 <sup>32</sup> Martins et al. 2020 <sup>39</sup>
10mGS	1. AWGS (2014) GS: <0.8 m/s (both genders).	Kosoku et al. 2020 <sup>41</sup> and Yanishi et al. 2018 <sup>45</sup>

Abbreviations: ALM, appendicular lean mass; ASMI, appendicular skeletal muscle index; AWGS, Asian Working Group for Sarcopenia; BIA, bioelectrical impedance analysis; BMI, body mass index; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older People; GS, gait speed; HGS, handgrip strength; LTI, lean tissue index; MMI, muscle mass index; SD, standard deviation; SMI, skeletal muscle mass index.

$I^2 = 12.1\%$ , two studies), infections (RR: 1.03, 95% CI: 0.34–3.12,  $I^2 = 87.4\%$ , two studies), delayed graft functions (RR: 0.81, 95% CI: 0.46–1.43,  $I^2 = 0.0\%$ , three studies), and death (RR: 0.95, 95% CI: 0.32–2.82,  $I^2 = 0.0\%$ , two studies) in KRTs (Figure 4).

### Publication bias

There was no publication bias in the prevalence of sarcopenia in this study (Begg's test:  $P = 0.054$ ; Egger's test:  $P = 0.093$ ).



**Figure 2** Prevalence of sarcopenia in kidney transplantation recipients. CI, confidence interval; ES, effect size (prevalence %). Random effects model used for analysis.

## Discussion

KT improves the quality of life and life expectancy of ESRD patients and has higher economic benefits compared with dialysis in CKD patients.<sup>1,58–62</sup> Every year, the number of elderly candidates for KT has been increasing.<sup>63</sup> Current guidelines recommend the assessment of frailty for the prospective KT candidates, whereas sarcopenia is ignored.<sup>2</sup> However, these two geriatric syndromes have many overlapping causes and consequences that may have significant implications in this particular clinical setting.<sup>64</sup> Patients with sarcopenia/LMM can lead to transplant failure, increased mortality, and postoperative complications such as systemic infection after KT.<sup>14,15,30,35</sup> Recent findings suggest that the mechanism of sarcopenia in KT candidates could be (i) nephropathy-related causes: nutritional deficiency and concomitant malnutrition,<sup>65</sup> vitamin D deficiency,<sup>66</sup> metabolic

acidosis,<sup>67</sup> insulin resistance,<sup>68</sup> low physical activity,<sup>69</sup> hyperparathyroidism,<sup>70</sup> uraemia,<sup>10</sup> and proteinuria<sup>71</sup>; and (ii) chronic low-grade inflammation that typical occurs in dialysis patients.<sup>72</sup> KT can correct or ameliorate some of the causes of sarcopenia, such as metabolic acidosis and chronic inflammation. But the post-transplant immunosuppressive drug usage, low physical activity, and poor renal function still can reduce muscle mass and function in KTR subjects.<sup>64</sup> Sarcopenic obesity is commonly diagnosed in KTR individuals and are associated with an increased risk of death, disability, cardiovascular diseases, and metabolic disorders.<sup>73</sup> This study summarized the prevalence, diagnostic criteria, clinical predictors, and outcomes of sarcopenia in KTRs.

We found that the overall prevalence of sarcopenia was 26% in KTRs, including 22% in men and 27% in women. A meta-analysis found that the prevalence of sarcopenia in ESRD patients undergoing dialysis was 28.5%.<sup>4</sup> Another

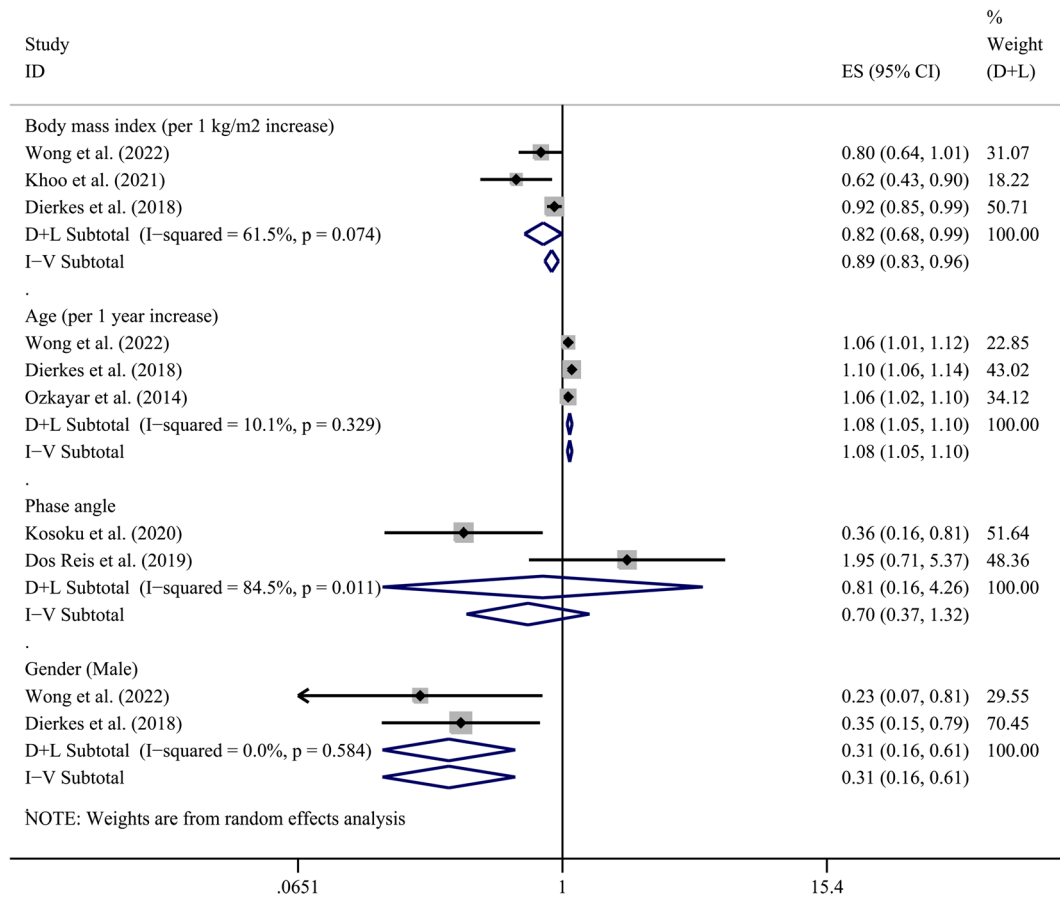


Figure 3 Clinical predictors of sarcopenia in kidney transplantation recipients. CI, confidence interval; ES, effect size (odds ratio).

Table 3 Clinical impact of the sarcopenia in different variables in KRTs

Categories	Variables	Compared with KTRs without sarcopenia	
		1 criterion	>1 criterion
Health-related quality of life	SF-36		Worse <sup>44</sup>
Physical activity level	Activity time	N.d. <sup>33</sup> (min/day)	Reduction <sup>44</sup> (h/week)
	Baecke questionnaire		Reduction <sup>42</sup>
Complications		N.d. <sup>6</sup>	
Postoperative ICU admission		N.d. <sup>29</sup>	
Early hospital readmission		N.d. <sup>29</sup>	
Inflammation	WCC, cells × 10 <sup>9</sup> /L	N.d. <sup>29</sup>	
	CRP (mg/L)	N.d. <sup>29</sup>	N.d. <sup>38,41</sup>

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; KTRs, kidney transplantation recipients; N.d., no significant difference; SF-36, Medical Outcomes Study Short Form-36 questionnaire; WCC, White cell count.

meta-analysis showed that in patients with CKD not yet on dialysis, the prevalence of sarcopenia was 34.5% in stages 2 and 3A of CKD and 65.5% in stages 3B, 4, or 5.<sup>74</sup> The prevalence of sarcopenia appears to be lower in CKD patients on dialysis or after KT, possibly due to a reduction in uraemic toxins and improved kidney function.<sup>10</sup> This can be further studied in the future. Meta-regression showed that the mean age and male percentage were not associated with the

prevalence of sarcopenia, suggesting the importance of assessing sarcopenia even in male and younger KTRs. Diagnosis of sarcopenia includes either the LMM alone or combined criteria of LMM and LMS and/or LPP. The prevalence of sarcopenia assessed by LMM alone was 34% compared with 21% by LMM with LMS and/or LPP. As reported in dialysis patients and chronic obstructive pulmonary disease patients,<sup>4,75</sup> the combined criterion exhibited a lower positive rate than



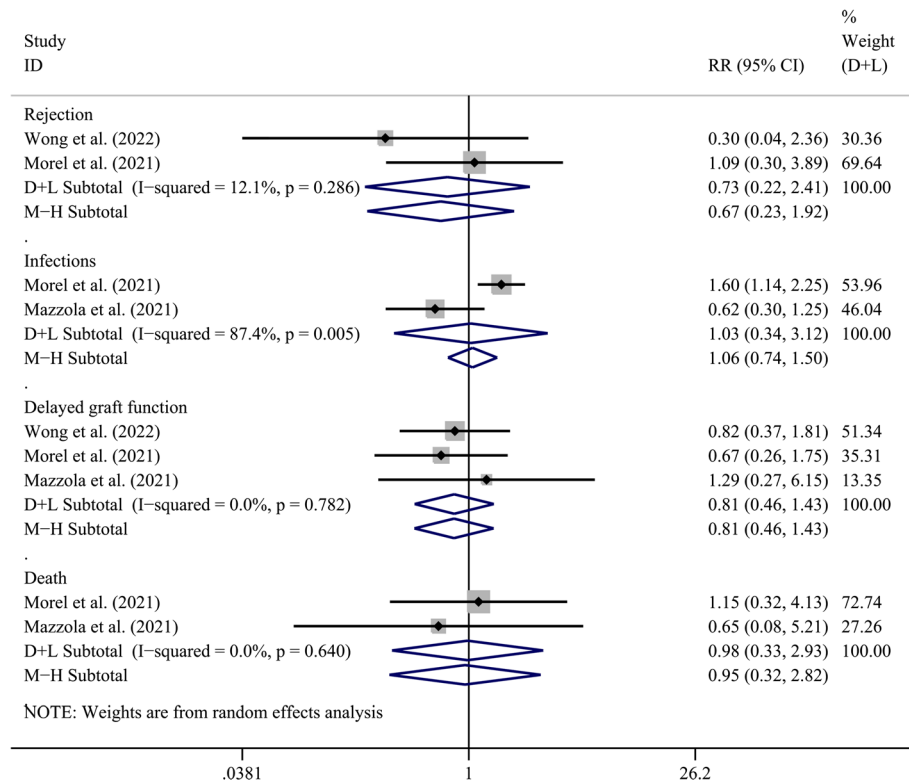


Figure 4 Clinical impact of sarcopenia in kidney transplantation recipients.

the LMM alone in the assessment of sarcopenia, but it improved the accuracy of the sarcopenia diagnosis, which is now internationally recognized as the standard assessment criterion. The prevalence of sarcopenia assessed by EWGSOP and AWGS was lower than that by other methods, which included LMM assessment by CT, may be a pre-requisite for presurgical anatomic mapping, and can be used to assess early and late-term post-transplant complications for KT patients,<sup>29,76</sup> but the resulting prevalence varies widely, ranging from 5.0%<sup>30</sup> to 72.1%<sup>6</sup> due to the use of different cut-off thresholds. It is recommended that future studies should use uniform CT cut-off thresholds to assess the LMM. For HGS and GS, the included studies used EWGSOP and AWGS diagnostic criteria, but the selection of cut-off thresholds and detection methods were uneven. It is recommended that future studies should count only the standardized cut-off thresholds and conduct consistent tests to diagnose sarcopenia.

Aging has been considered a risk factor for sarcopenia in KTRs. Previous studies have shown that advanced aging is the most important risk factor for sarcopenia.<sup>77</sup> However, average age did not affect the prevalence of sarcopenia in our meta-regression, suggesting that even young patients should be screened for sarcopenia. Malnutrition is an important risk factor for sarcopenia,<sup>78</sup> and BMI is one of the most commonly used and easily accessible indicators of nutritional status in clinical practice.<sup>79</sup> Many studies reported that BMI

was the best predictor of sarcopenia.<sup>41,45</sup> We found that lower BMI is a risk factor for sarcopenia, which can be used to predict the risk of sarcopenia in KTRs. Studies have confirmed that overweight and obesity in KTRs are known problems.<sup>80–82</sup> Excessive fat deposition and muscle loss are common in patients after KT, a condition known as sarcopenic obesity.<sup>83–86</sup> The assessment of fat mass requires a combination of BMI and body composition or abdominal circumference.<sup>5,87</sup> Previous studies have shown that weight gain is often observed in the early post-transplant period, but this change in weight is not due to an increase in muscle mass, but rather an increase in fat mass. Conversely, muscle mass may decrease even further in the short term after KT.<sup>88</sup> Even within 2 years after KT, the increase in fat mass in KTRs was significantly greater than the increase in muscle mass.<sup>34,89</sup> Taken together, existing studies have found that an increase in BMI contributes to a lower risk of sarcopenia, whereas an increase in body fat mass can lead to muscle loss, helping to partially explain the 'obesity paradox'.<sup>86</sup> Therefore, KTRs should increase physical activity, perform muscle training and dietary control to increase BMI, and reduce body fat mass to prevent the development of sarcopenia.<sup>89–91</sup> In contrast to women, men were a protective factor for sarcopenia. However, meta-regression found that the percentage of male subjects was not associated with the prevalence of sarcopenia, suggesting that even men should be evaluated for

sarcopenia. Dos Reis *et al.*<sup>43</sup> showed that phase angle was only related to the HGS, but not to sarcopenia in KTRs, whereas Kosoku *et al.*<sup>41</sup> reported the opposite. The pooled results revealed that phase angle was not associated with sarcopenia, but this result should be generalized with caution due to the availability of a small number of studies. Furthermore, it has been reported that creatinine,<sup>29</sup> mean muscle attenuation of the total muscle,<sup>29</sup> inorganic phosphates (PO<sub>4</sub>),<sup>29</sup> vascular reactivity index (VRI),<sup>32</sup> polyunsaturated fatty acid,<sup>33</sup> ω-3 fatty acids,<sup>33</sup> albumin,<sup>8</sup> and obesity<sup>8</sup> were protective against sarcopenia. Parathyroid hormone (PTH),<sup>29</sup> glucocorticoids,<sup>34</sup> fat mass index (FMI),<sup>34</sup> wound complications,<sup>35</sup> the combined endpoint of graft loss and/or death,<sup>35</sup> glomerulonephritis,<sup>8</sup> pre-transplantation sarcopenia,<sup>8</sup> physical health-related QoL,<sup>44</sup> mental health-related QoL,<sup>44</sup> and prescribed medications<sup>47</sup> were risk factors for sarcopenia. Regarding muscle strength, Chan *et al.*<sup>44</sup> found that lean tissue index, age, male sex, haemoglobin count, vitamin D level, physical activity level, and protein intake were the associated risk factors. Whereas Khoo *et al.*<sup>32</sup> showed that only VRI was related to the HGS.

Sarcopenia has a negative impact on clinical outcomes related to KTRs, including quality of life, physical activity levels, graft rejection, systemic infection, delayed graft function, and death. Oterdoom *et al.* found that muscle mass was negatively associated with KTRs death and graft loss.<sup>14</sup> Sterja *et al.* found a negative association between muscle mass and death among KTRs.<sup>15</sup> Deliege *et al.* showed that LMM was associated with the longer hospital stays after KT, higher rates of wound complications, and graft loss or death in the elderly male patients.<sup>35</sup> Wong *et al.* found that after adjusting for the age, sex, dialysis vintage, type of transplant, length of hospital stay for KT admission, delayed graft function, diabetes, and rejection within the first month of KT, the risk of readmission within 30 days after KT in sarcopenia patients was 7.22 times higher than in patients without sarcopenia (95% CI: 1.87–27.91).<sup>29</sup> Included studies showed mortality rates of 20%,<sup>30</sup> 10.2%,<sup>35</sup> and 10%<sup>44</sup> in sarcopenia patients after KT. Chan *et al.* reported that after adjustment for age, sex, ethnicity, smoking habit, and alcohol consumption, post-KT sarcopenia patients had a 1.94-fold (95% CI: 1.10–3.42) higher risk of death and acute hospitalization than those without sarcopenia.<sup>44</sup> However, due to the limited data provided by the included studies, this study could not clarify the relationship between them. In the future, larger cohorts and multicentre studies are needed to determine negative controls to explore the clinical effects of sarcopenia on KTRs and to set up an intervention group for sarcopenia, as well. And there is currently a void in this field. We were unable to demonstrate a relationship between sarcopenia and inflammatory biomarkers. Wong *et al.*, Menna Barreto *et al.*, and Kosoku *et al.* found no difference in the level of CRP and white blood cell count between sarcopenic and non-sarcopenic KT recipients.<sup>29,41,42</sup> Although we could not

detect the involvement of any specific inflammatory factor related to sarcopenia, however, our study showed that sarcopenia could be associated with increased secretion of pro-inflammatory cytokines (e.g., tumour necrosis factor α and interleukin-6),<sup>92</sup> which seemed to be a valuable area for future research.

To our knowledge, this systematic review was the first to compare the diagnostic methods, prevalence, clinical predictors, and clinical impact of sarcopenia in KTRs. We provided a comparative analysis of commonly used diagnostic criteria for sarcopenia in the KT population and summarized the prevalence rates reported in the recent studies to provide a basis for future interventions. At the same time, we described the influencing factors of sarcopenia in KTRs. Given the aforementioned risk factors, early risk assessment and intervention should be prioritized to prevent the occurrence of sarcopenia, as well as to reduce its adverse impacts on the prognosis of KTRs. Finally, our study analysed the impact of sarcopenia on the prognosis of KT. Although the included studies were limited in number and the impact could not be accurately estimated, they still provide some fundamental clues for future investigations. We found that sarcopenia was highly associated with increased mortality and early readmission rates in KTRs. We thus recommend widespread early screening and guidance for the prevention and treatment of sarcopenia to improve outcomes and reduce the burden of family and social care on patients.

There are certain limitations to this study. First, the included studies had significant heterogeneity ( $I^2 = 93.45\%$ ), mainly in terms of diagnostic methods, measurement methods, diagnostic thresholds, and participants' characteristics, for which we performed the subgroup analysis, meta-regression, and sensitivity analysis to find the possible sources of heterogeneity. Second, for the clinical predictors and their impacts on sarcopenia after KT, the number of studies on some variables was limited, and so the application and promotion of the combined results were also restricted to a certain extent. Finally, we did not include meta-analyses of studies on the relationship between muscle mass, as reflected by creatinine levels, and prognosis in kidney transplant recipients, which was determined by inclusion criteria. Yanishi *et al.*<sup>93</sup> found that the creatinine/cystatin C ratio is suitable for evaluating muscle mass in KTRs. However, they did not explore its impact on the prognosis of KTRs. Future studies could use the creatinine/cystatin C ratio as one of the biomarkers reflecting muscle mass to predict transplant outcomes.

## Conclusions

In conclusion, due to the high prevalence of sarcopenia among KTRs, it is important to screen and evaluate

sarcopenia at an early stage, and standardization of diagnostic criteria for sarcopenia in KTRs would be beneficial in the future. Large study cohorts and multicentre longitudinal studies are urgently needed to explore the prevalence and prognosis of sarcopenia in kidney transplant patients.

## Conflict of interest

All authors have no conflicts of interest to disclose.<sup>94</sup>

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## 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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