



Polypharmacy and sarcopenia in patients on hemodialysis: results from the SARC-HD study

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Abstract

Background We investigated the association between polypharmacy and sarcopenia in patients on hemodialysis.

Methods Cross-sectional data from the SARC-HD study were analyzed. Patients were classified according to the number of prescribed medications as no polypharmacy (0–4), polypharmacy (5–9), and hyperpolypharmacy (≥ 10). Sarcopenia was diagnosed and staged according to the adapted EWGSOP2 consensus.

Results 955 patients (48% ≥ 60 years, 61% male) were analyzed. Polypharmacy and hyperpolypharmacy were observed in 50% and 26% of patients, respectively. Patients with hyperpolypharmacy had poorer physical function compared to the no polypharmacy group. Low muscle strength was found in 45%, while sarcopenia (confirmed and severe stages) in 21% of the cohort. Patients in the polypharmacy groups had higher prevalence of low muscle strength, but similar sarcopenia rates to those in the no polypharmacy group. Only hyperpolypharmacy was independently associated with low muscle strength (64% higher adjusted odds, 95% CI 1.10–2.46), whereas no significant associations were observed with sarcopenia. Also, each addition of two medications was independently associated with 10% higher adjusted odds (95% CI 1.02–1.20) of low muscle strength.

Conclusions In patients on hemodialysis, the number of medications and hyperpolypharmacy were independently associated with low muscle strength, but not with sarcopenia per se.

Keywords Chronic kidney disease · End-stage kidney disease · Frailty · Handgrip strength · Drug therapy · Medication

Marvery P. Duarte and Nicolle P. Marinheiro contributed equally and shared the first author's position.

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Introduction

Chronic kidney disease (CKD) accelerates or worsens aging-related phenotypes and is associated with multiple comorbidities, including hypertension, diabetes, anemia, mineral bone disorder, and cardiovascular diseases [1]. Therefore, to manage and mitigate multimorbidity and symptoms [2], the concomitant use of multiple medications, known as polypharmacy, is expected [3]. The prevalence of polypharmacy in people with CKD is over 80% and higher in those undergoing dialysis [4]. Polypharmacy is associated with a lower quality of life, medication non-adherence, and higher mortality risk [4].

Similarly, sarcopenia – a skeletal muscle disease characterized by low levels of muscle strength and muscle mass – [5] affects 29% of patients on hemodialysis [6] and increases mortality risk [7]. Both polypharmacy and sarcopenia are frequently observed in older age groups and in patients with advanced CKD; however, their association remains to be explored. Thus, this study aimed to investigate the association between polypharmacy and sarcopenia in a large multicenter cohort of patients on hemodialysis.

Methods

Design, setting, and population

This is a cross-sectional report of the **SARC-HD** (*SARCopenia trajectories and associations with clinical outcomes in patients on HemoDialysis*) study, a large national multicenter prospective cohort, conducted at 19 dialysis centers across Brazil since October 2022. A detailed description of the study design and methodology has been published elsewhere [8]. Briefly, patients ≥ 18 years old undergoing maintenance hemodialysis for $\geq$ three months were eligible for participation. The exclusion criteria for this report included missing data on handgrip strength and a lack of medication prescriptions in the electronic health records. All participants provided written informed consent. The study was approved by the research ethics committees and conducted in adherence to the conditions of the Declaration of Helsinki. This manuscript was written in accordance with the STROBE guidelines.

Sociodemographic and clinical variables

Clinical (comorbidities, CKD etiology etc.) and demographic data were collected from the electronic health records by an experienced researcher at each dialysis center.

Polypharmacy

Medication records, including drug name and class, were obtained from the electronic health records of each participant (Supplementary Table S1) and, when necessary, confirmed by the patient's nephrologist. Only allopathic medications continuously administered during the current and past month preceding the interview were considered, with each active ingredient classified according to the Anatomical Therapeutic Chemical Dictionary. For combination drugs, each active ingredient was considered a separate medication. Polypharmacy was considered as the daily concomitant use of ≥ 5 medications (active ingredients) excluding those prescribed within the dialysis session, *e.g.*, heparin. Patients were then categorized into three groups: no polypharmacy (0–4 medications), polypharmacy (5–9) and hyperpolypharmacy (≥ 10). These categories were adopted based on previous studies from a recent systematic review on CKD [4].

Sarcopenia diagnosis

Physical function and muscle mass measurements were performed before and after a midweek dialysis session, respectively. A detailed description of the protocol was published previously [8]. Sarcopenia diagnosis algorithm and staging were based on the revised European Working Group on Sarcopenia in Older People (EWGSOP2) [9] as no sarcopenia, probable sarcopenia (low muscle strength only, *i.e.*, handgrip strength < 27 kg for males; < 16 kg for females or five-time sit-to-stand test > 15 s for both sex), confirmed sarcopenia (low muscle strength *in addition to* low muscle mass, *i.e.*, calf circumference ≤ 34 cm for males; ≤ 33 cm for females), and severe sarcopenia (confirmed sarcopenia *plus* low physical performance, *i.e.*, gait speed ≤ 0.8 m/s for both sex). In patients with missing data for calf circumference or gait speed, only the probable sarcopenia stage was assessed. Handgrip strength data was available for all patients.

Statistical analysis

Data imputation was not performed for variables of interest (sarcopenia and polypharmacy). However, we imputed descriptive variables considered as confounders (missing body mass index = 9, dialysis modality = 1, and comorbidities = 1) by applying the multiple imputation regression method. Age and sex were used as predictors, whereas the variables of imputation interest were not.

Normality of data was assessed by visual inspection of histograms and the Kolmogorov–Smirnov test. Comparisons among groups based on polypharmacy were conducted using the Kruskal–Wallis or one-way ANOVA with Dunnett's post-hoc correction (reference = no polypharmacy) test for

continuous variables and the Chi-Square or Fisher Exact tests for categorical variables.

Binary logistic regressions were conducted to investigate the association between polypharmacy (reference = no polypharmacy) and sarcopenia (confirmed *plus* severe stages) and its traits. We considered confirmed and severe sarcopenia groups as ‘sarcopenia’, as there were only a few cases of severe sarcopenia (5%). Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Clinically relevant confounders to be adjusted were selected by creating a Directed Acyclic Graph (see Supplementary Fig. 1). Adjusted model included older age (reference ≤ 60 years), male sex, ethnicity (reference = non-white), body mass index (continuous), vascular access (reference = arteriovenous fistula), and number of comorbidities (reference = 0). Subgroup analyses were conducted according to age (< 60 and ≥ 60 years) and sex. Analyses were performed using the Statistical Package for the Social Sciences (version 29.0, SPSS Inc, Chicago, IL, USA). Statistical significance was set at a two-tailed p -value < 0.05 .

Results

Patients’ characteristics

A total of 1525 patients were assessed for eligibility, with 1008 recruited and 955 included in this study (Supplementary Figure S2). The majority of patients were male (61%) and 48% were ≥ 60 years. The median dialysis vintage was 33 [interquartile range (IQR):14–65] months, 22% of patients had ≥ 3 comorbidities, and most were receiving conventional hemodialysis (68%).

Polypharmacy status

Median number of medications was 7 (IQR: 5–10; see the histogram in Supplementary Figure S3). Polypharmacy and hyperpolypharmacy were observed in 50% and 26% of the cohort, respectively. The distribution of the most common drug classes across polypharmacy groups is presented in Supplementary Table S2. Comparisons among groups are described in Table 1. Patients with hyperpolypharmacy were older, had more comorbidities, poorer physical function performance, and higher ferritin levels, but had similar muscle mass compared to the no polypharmacy group.

Prevalence of sarcopenia and its traits

Low muscle strength, low muscle mass, and low physical performance were found in 45%, 43%, and 17% of the cohort, respectively. A significant difference was only observed in low muscle strength, which was higher in the

polypharmacy groups ($p = 0.002$; Fig. 1A). A total of 12%, 9%, and 5% had probable, confirmed, and severe stages of sarcopenia, respectively. No significant difference was observed for the prevalence of sarcopenia stages among the polypharmacy groups (Fig. 1B), even combining the confirmed and severe stages ($p = 0.301$).

Association between polypharmacy and sarcopenia

Binary logistic regressions results are presented in Supplementary Table S3 and show that hyperpolypharmacy was independently associated with low muscle strength (adjusted OR [aOR] = 1.64, 95% CI 1.10–2.46). In contrast, no significant association was observed between hyperpolypharmacy and low muscle mass, low physical performance, nor sarcopenia in both unadjusted and adjusted models. By treating the number of medications as a continuous variable, each increase of two medications was independently associated with 10% higher odds for low muscle strength (aOR = 1.10, 95% CI: 1.02 – 1.20). Subgroup analyses based on sex and age showed similar results. However, the overall association between hyperpolypharmacy and low muscle strength was only confirmed in females (aOR = 2.54, 95% CI 1.31–4.92) and older adults (aOR = 1.80, 95% CI 1.02–3.17), whereas no significant associations were observed in males (aOR = 1.24, 95% CI 0.74–2.08) or those aged < 60 years (aOR = 1.36, 95% CI 0.75–2.45).

Discussion

To the best of our knowledge, this is the first study to investigate the association between polypharmacy and sarcopenia in patients on hemodialysis. Although no differences were observed in the prevalence of sarcopenia among the polypharmacy groups, suggesting that the number of medications alone may not be directly associated with the clinical diagnosis of sarcopenia, patients with hyperpolypharmacy had a 64% higher likelihood of presenting with low muscle strength. Furthermore, patients with hyperpolypharmacy group exhibited poorer physical function compared to those without polypharmacy. Our original findings highlight that the number of medications is associated with low physical function, demonstrating hyperpolypharmacy as a concerning condition that may contribute to sarcopenia.

Our findings contribute to growing concerns regarding polypharmacy in patients with CKD [10, 11], suggesting that hyperpolypharmacy may contribute to low muscle strength, but not to low muscle mass. Although muscle strength and muscle mass are interrelated, they represent distinct physiological domains [12]. This discrepancy may be explained by the fact that muscle strength is a more sensitive and functional marker of neuromuscular integrity, whereas muscle

Table 1 Sociodemographic and clinical characteristics of the patients on hemodialysis according to the polypharmacy status

	No polypharmacy	Polypharmacy	Hyperpolypharmacy	<i>p</i> -value
n (%)	236 (24.7)	475 (49.7)	244 (25.5)	
Female	80 (33.9)	194 (40.8)	102 (41.8)	0.136
Age (years)	56.0 ± 15.3	57.3 ± 15.4	59.7 ± 14.3 ^a	0.024
≥ 60 years, n (%)	99 (41.9)	225 (47.4)	135 (55.3)	0.012
Ethnicity, n (%)				0.670
White	104 (44.1)	226 (47.6)	112 (45.9)	
Non-white	132 (55.9)	249 (52.4)	132 (54.1)	
Comorbidities, n (%)				
Diabetes	59 (25.0)	194 (40.9)	144 (59.3)	< 0.001
Hypertension	179 (75.8)	400 (84.2)	218 (90.1)	< 0.001
Cancer	12 (5.1)	22 (4.6)	14 (5.8)	0.803
COPD	7 (3.0)	12 (2.5)	13 (5.4)	0.127
Heart failure	29 (12.3)	68 (14.3)	54 (22.3)	0.005
CAD	29 (12.3)	83 (17.5)	62 (25.6)	0.001
Neuropathies	17 (7.2)	33 (7.0)	27 (11.2)	0.131
No. of comorbidities, n (%)				< 0.001
0	43 (18.2)	39 (8.2)	9 (3.7)	
1–2	157 (66.5)	337 (70.9)	156 (64.2)	
≥ 3	36 (15.3)	99 (20.8)	78 (32.1)	
No. of medications, median [IQR]	3 [2–4]	7 [6–8]	11 [10–13]	< 0.001
Ferritin (ng/mL)	229 [92–376]	233 [111–424]	257 [125–410] ^a	0.033
Dialysis modality, n (%)				0.832
Conventional	157 (66.5)	326 (68.8)	166 (68.0)	
Hemodiafiltration	79 (33.5)	148 (31.2)	78 (32.0)	
Dialysis vintage (months)	36 [14–73]	31 [12–62]	33 [17–63]	0.208
Vascular access, n (%)				0.354
Arteriovenous fistula	184 (78.0)	351 (73.9)	177 (72.5)	
Catheter	52 (22.0)	124 (26.1)	67 (27.5)	
Body composition				
Body mass index (kg/m ²)	25.2 ± 5.1	25.8 ± 4.7	26.3 ± 5.5	0.061
Calf circumference (cm)	35.0 ± 4.0	34.6 ± 3.8	34.4 ± 4.2	0.299
Physical function				
Handgrip strength (kg)	29.3 ± 10.2	27.5 ± 10.3 ^a	26.3 ± 9.4 ^a	0.004
Gait speed (m/s)	1.14 ± 0.36	1.11 ± 0.33	1.05 ± 0.37 ^a	0.024
Five-time sit-to-stand (seconds)	12.6 ± 5.9	12.6 ± 4.7	14.5 ± 5.5 ^a	< 0.001
Engaged in an exercise program, n (%)	70 (29.7)	157 (33.1)	84 (34.4)	0.509

CAD coronary artery disease, COPD chronic obstructive pulmonary disease, CKD chronic kidney disease, IQR interquartile range

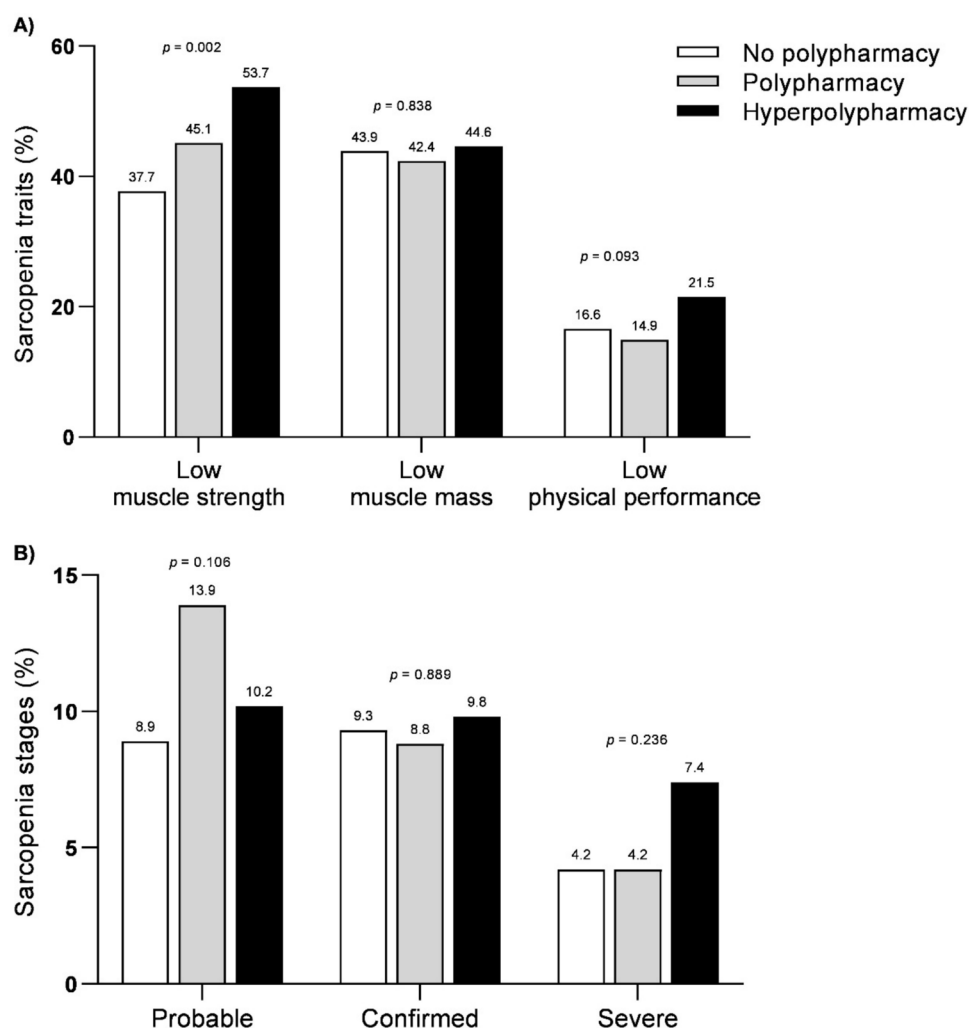
^aIndicates a significant difference compared to the no polypharmacy group

mass alone does not necessarily reflect muscle quality or function [13]. Thus, we believe that the absence of an association between polypharmacy and muscle mass does not preclude clinically meaningful neuromuscular impairment. Instead, it underscores the importance of prioritizing muscle strength assessments such as handgrip strength or five-time sit-to-stand test in clinical practice and future research.

Most studies in this field have focused on non-CKD adults [14], but our findings suggest that this association persists among patients on hemodialysis. Managing inappropriate

medications prescriptions, which leads to polypharmacy, should be a priority for clinicians treating patients with multiple comorbidities (*e.g.*, end-stage kidney disease), given its potential impact on health outcomes, such as higher hospitalization risk, bleeding rate, and all-cause mortality risk [11]. Our novel findings show that hyperpolypharmacy may also interact with poor physical function, which is an independent risk factor for all-cause mortality in CKD [7]. Thus, effective strategies to reduce the medication burden may enhance CKD care by mitigating the adverse effects

Fig. 1 Prevalence of sarcopenia and its traits according to the polypharmacy status. **A** sarcopenia traits; **B** sarcopenia stages



associated with hyperpolypharmacy, including low muscle strength. Integrating clinical pharmacists into dialysis teams may help reduce the burden of polypharmacy and help to improve clinical outcomes.

Previous studies have focused on frailty, geriatric syndrome that shares similarities with sarcopenia (*e.g.*, low muscle strength as a component). Kimura et al. found that hyperpolypharmacy (> 11 medications) was associated with frailty and its incidence over a 2-year follow-up period [15]. Similarly, Takeuchi et al. found that the number of medications a patient was taking was independently associated with frailty prevalence [16]. Chan et al. reported that the number of prescribed medications, a surrogate for polypharmacy, predicted the onset and progression of frailty and malnutrition in patients on peritoneal dialysis [17]. Collectively, these findings corroborate ours regarding the negative impact of polypharmacy on fitness and physical function.

Although a significant association between hyperpolypharmacy and low muscle strength was observed in our study, the subgroup analysis revealed that this was only present

in older adults and females. Younger adults tend to take fewer medications, and polypharmacy is less common in this group, which may explain why the association was only observed in those aged ≥ 60 years. Regarding the females, they are particularly at a higher risk for polypharmacy [18], therefore, the impact on physical function may be more pronounced in this population group.

Future studies should focus on the mechanisms underlying this phenomenon, particularly how the side effects of medication may impair the ability of the neuromuscular system to generate strength [19]. Furthermore, studies examining the effects of different drug classes on muscle strength and the development of sarcopenia are essential.

The strengths of our study rely in its multicenter design and real-world recruitment from dialysis centers across three regions and five states of Brazil, which may partially represent the Brazilian population on hemodialysis. Importantly, the cross-sectional design of our analysis precludes causal inference. Although polypharmacy may contribute to reduced muscle strength and consequently to

the development of sarcopenia through pharmacological mechanisms, it is also plausible that patients with sarcopenia may present with a greater burden of comorbidities, thereby increasing the likelihood of multiple medication use. Therefore, reverse causation is a possibility and should be carefully considered when interpreting our findings. Additionally, the lack of detailed information regarding medication dosage, treatment duration, and adherence to prescriptions are important limitations that warrants further investigation through longitudinal studies. In addition, we used the calf circumference as a proxy for muscle mass, which may yield less reliable results compared to “gold standard” methods.

Conclusions

In our large multicenter cohort of patients on hemodialysis, the number of medications and hyperpolypharmacy were independently associated with low muscle strength, but not with sarcopenia per se. As low muscle strength is a hallmark of sarcopenia, this suggests that interventions aimed at improving muscle strength should consider the number of prescribed medications as a key factor to be addressed to optimize patient outcomes.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40520-025-03101-9>.

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Author contributions MPD, MMR, MWP, and HSR designed the study. HSR and MPD analyzed data. MPD, NPM, and HSR wrote the manuscript. All authors substantively contributed to data collection and methodology, revised the content and results of the manuscript, read, reviewed, and approved the final version.

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Data availability Data is available upon reasonable request to the corresponding author (HSR).

Declarations

Conflict of Interest The authors declare no competing interests.

Ethical approval This study was performed in accordance with the ethical standards and was ethically appraised by the Institutional Review Board of the University Center ICESP (no. 5.418.365; all other insti-

tutional review boards reviewed and agreed with the approval letter), which adheres to the Declaration of Helsinki.

Informed consent All participants provided written informed consent.

Generative AI-assisted technologies During the preparation of this work, the authors used ChatGPT in order to rephrase content previously published by our study group on the same project. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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