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Original Article

ORIGINAL ARTICLE

Quality matters: chronic kidney disease progression is associated with reduced muscle strength independently of changes in skeletal muscle mass: an observational study

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ABSTRACT

Background. Chronic kidney disease (CKD) is commonly associated with multifactorial neuromuscular impairments. Few studies have investigated CKD-induced changes in maximal voluntary force (MVF), and even fewer have longitudinal follow-up. The aim of this study is to investigate whether CKD progression modifies the relationship between skeletal muscle mass and force, and the prevalence of sarcopaenia and sarcopenic obesity.

Methods. The data used were prospectively collected during routine check-ups in a network of nutritional centres in Mexico and retrospectively analysed. From a dataset of 5430 patients, we selected 1098 patients with available anthropometric, kidney function, handgrip and bioimpedance data. The relationship between appendicular skeletal muscle mass (ASM) and MVF was investigated using mixed models and adjusted for age, sex, body mass index, physical activity level and CKD aetiology. Sarcopaenia prevalence were tested across period of follow-up using the Cochran–Mantel–Haenzen for repeated measures and across CKD stages using the Chi-2 test.

Results. After normalization with ASM, MVF was higher in CKD G1–G3 compared with G4 and G5 ($P \leq .001$, Cohen's d = 0.270–0.576). Slopes between MVF and ASM were lower in CKD G3, G4 and G5 than in CKD G1–G2 [–2.268 (–3.927, –0.609), $P = .008$; –2.694 (–4.593, –0.794), $P = .006$; –3.675 (–5.326, –1.725), $P < .001$, respectively]. The prevalence of sarcopaenia and sarcopaenic obesity did not differ across CKD stages, but recovery was most commonly observed in CKD G1–G2. Slope analysis showed an independent interaction between the slopes of kidney function and ASM on MVF evolution over time.

Conclusions. CKD negatively, progressively and independently affects the neuromuscular system, and force production is reduced for any given muscle mass as CKD progresses. While no association was found between CKD stage and prevalence of sarcopaenia, recovery was more frequent in the early CKD stages. These results suggest the importance of early rehabilitation programs to improve musculoskeletal health, quality of life and survival in CKD patients.

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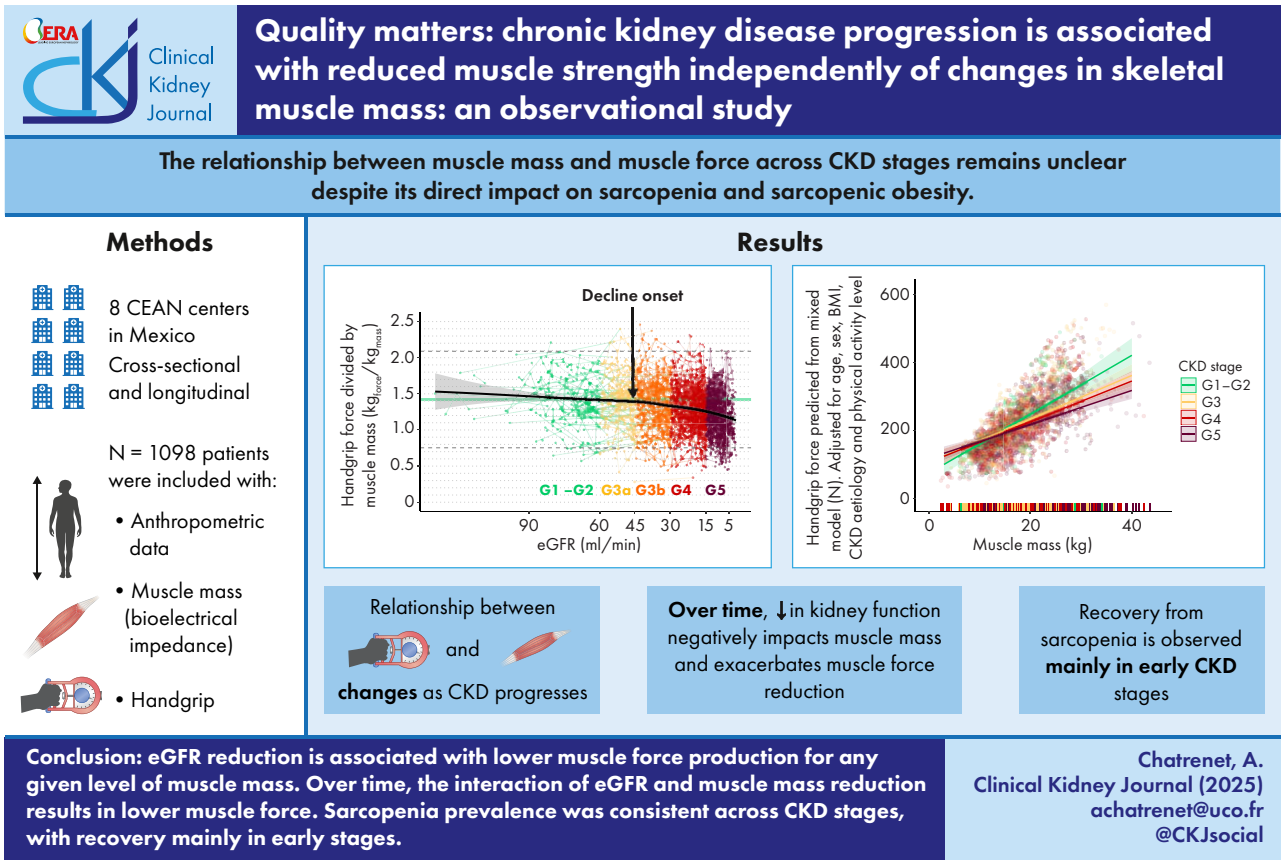
GRAPHICAL ABSTRACT



Keywords: kidney cachexia, musculoskeletal health, nutritional status, sarcopenia, skeletal muscle

INTRODUCTION

The association between chronic kidney disease (CKD) and impairment of neuromuscular function is well acknowledged [1–4], as is the negative effect that CKD has on exercise tolerance [5] and on survival [6]. Consequently, muscle strength is commonly assessed in both research and clinical practice on the basis of a handgrip task [7–9].

Muscle strength is usually found to be lower in CKD patients than in age-matched non-CKD peers [10]. In addition, CKD is associated with neurological impairment [11–13], skeletal muscle fat infiltration [14], mitochondrial, inflammation, uraemic toxins and hormonal imbalance [10, 15] reducing physical performance [16] and limiting muscle strength production. Recently, studies in muscle fibre of CKD mice showed a –36% to –51% reduction in force production for a given cross-sectional area compared with control mice [17]. This dissociation between muscle mass and force may be the basis of the increased risk of sarcopaenia and sarcopaenic obesity in CKD [18], even though their relationship to CKD progression is not fully elucidated [19].

In the context of a multifactorial impairment, the relationship between impaired kidney function and muscle strength is unclear and few studies have addressed the relationship between muscle strength and kidney function [20, 21]. The cross-sectional study design is the one most commonly used. In addition, despite an expected association between kidney function and muscle strength, information regarding muscle mass and its evolution over time is scarce. Evidence confirming that such a relationship exists is needed as in CKD patients force production does not rely only on muscle mass [1, 3, 4, 17]. Thus, clarifying the evolution across CKD stages and better delineate the decline of the relationship between muscle mass and muscle force would allow to shed light on the importance of screening muscle force and may help clinicians to better anticipate sarcopaenia and frailty conditions.

The primary aim of our study was to investigate whether the impairment in force associated with reduced kidney function can be attributed to a reduction in muscle mass. The secondary aim was to determine whether the prevalence of sarcopaenia and sarcopaenic obesity increases across CKD stages. We first hypothesized a reduction of muscle force production with CKD stage independently of muscle mass changes. Secondly, we hypothesized an increase of sarcopaenia and sarcopaenic obesity prevalence with CKD severity.

MATERIALS AND METHODS

Study design and setting of care

The study is retrospective and observational. It employs anonymized data in the centre database that was gathered during routine clinical practice [22]. The overall cohort consists of

KEY LEARNING POINTS

What was known:

- Chronic kidney disease (CKD) impairs neuromuscular function, leading to reduced muscle force production and an increased prevalence of sarcopaenia, with no clear effect on the prevalence of sarcopaenic obesity.
- Recent murine models have detailed a dissociation between muscle fibre size and force production in the context of CKD—in other words, CKD-related muscle force impairment results from multifactorial physiological processes beyond just the reduction of muscle mass.

This study adds:

- The force production per unit of muscle mass is reduced as CKD progresses, independently of age, sex, body mass index, CKD aetiology and physical activity levels.
- Together, the decline of both glomerular filtration rate and muscle mass negatively affects muscle force.
- Although no association was found with CKD severity and sarcopaenia and sarcopaenic obesity prevalence, recovery was more frequently observed in the early CKD stages.

Potential impact:

- Since the present results demonstrated a CKD-related impairment in the ability of muscle mass to produce force, investigating multiple determinants of force production (e.g. voluntary activation, intramuscular processes) and their implication in muscle force reduction appears essential to better delineate neuromuscular limitations in CKD.
- In addition to maximal voluntary force assessment, research should explore various functional parameters (e.g. rate of force development, sit-to-stand test) under different conditions, such as during fatiguing exercises, in order to provide more comprehensive insights.
- It is essential to promote rehabilitation programs aimed at improving muscle function and quality. These programs should include physical exercises addressed to patients with preserved muscle mass and ideally started in early CKD stages, in order to improve or preserve musculoskeletal health.

patients without kidney replacement therapy receiving at least one consultation in one of the eight 'Centros de attention nutritional' (CEAN, Centers of nutritional attention) in Mexico (one each in Guadalajara, Monterrey, Pachuca, Puebla, Villahermosa and Tijuana, and two in Mexico City). The centres were founded by Fresenius Kabi to provide CKD patients with dietary consultations. Patient information were monitored at each consultation excepted for height, sex, educational level, CKD aetiology and physical activity level which were considered constant from the initial visit.

Selection of the study population

The selection of the study population is described in Fig. 1. After eliminating from the original dataset cases that lacked essential data (age, date of first consultation, kidney function; 24 767 observations and 5430 adult patients), the initial dataset included 23 927 observations (5162 patients), for a total follow-up of 3906 patient years.

Based on this initial dataset, a first selection (i.e. determining the final dataset) was performed to answer the working hypothesis, and a subsequent selection was made to perform the slope analysis, as follows (Fig. 1):

- Exclusion of observations of patients missing height, weight, handgrip or bioelectrical impedance assessment; this produced a final dataset of 2490 observations (1098 patients, 435 patient years).
- In order to perform the slope analysis, the requisite was for the patient to have had 6 months follow-up and that information on estimated glomerular filtration rate (eGFR), maximal voluntary force (MVF), appendicular skeletal muscle mass (ASM) and physical activity level had been recorded. This selection consists of 137 patients with 547 observations.

Glomerular filtration rate estimation

CKD was defined and staged in keeping with the KDIGO guidelines. As recommended, eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation in removing body surface area [23], calculated in accordance with the Du Bois and Du Bois (1916) formula [24]. The reference group was composed of G1–G2 CKD patients.

Bioelectrical impedance protocol

Bioelectrical impedance analysis [7] employed multifrequency bioelectrical impedance devices, using the SECA mBCA 514 (SECA, Co., Hamburg, Germany) or the Avis 333 Plus Segmental Body Composition Analyzer (Jawon Medical, Seoul, South Korea) depending on centre. Individuals were asked to stand in the orthostatic position during the whole-body analysis. ASM and fat mass (FM) were estimated both in absolute terms (kg) and in relation to body mass (%) [7].

Handgrip strength protocol

The Takei T.K.K.5401 GRIP-D handgrip dynamometer (Takei Scientific Instruments Co., Tokyo, Japan) was used to assess handgrip force. Patients were asked to stand in an upright position with the dynamometer in their dominant hand (the one used for writing) and their arm in a vertical position. When a vascular access was present (e.g. an arterio-venous fistula), the contralateral arm was tested. Patients were then told to squeeze the dynamometer as hard as possible and maintain their grip for 5 s. Three measures were recorded and the MVF obtained for analysis was the average of the three. MVF was analysed in Newton (N) units and normalized to ASM (kg of MVF/kg of ASM;

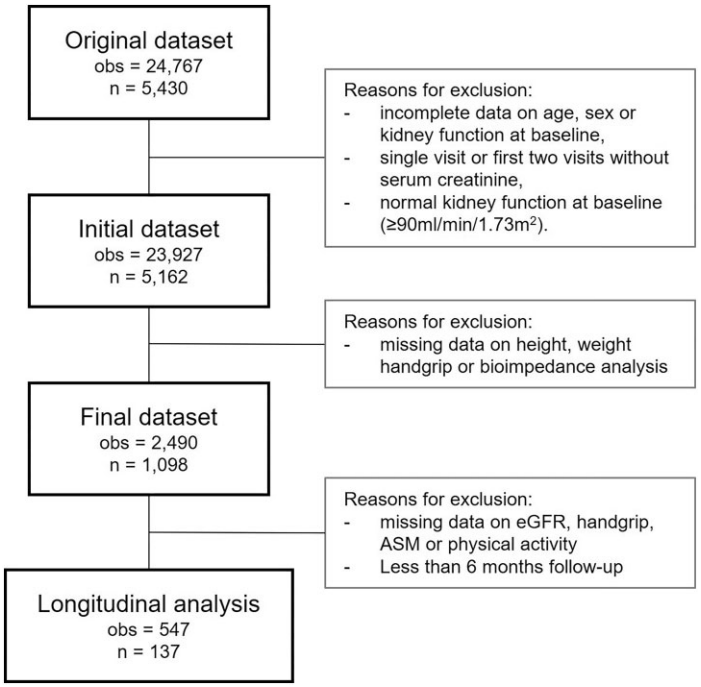


Figure 1: Selection of the study group population. obs: observations; *n*: number of patients.

MVF_{ASM}) to better reflect the force produced in relation to muscle mass.

Definitions

Both sarcopaenia [25] and sarcopaenic obesity [26] were defined as recommended by the European Working Group on Sarcopaenia in Older People (EWGSOP-2) [25]. Probable sarcopaenia was defined as low handgrip strength (i.e. <26 kg in males and <16 kg in females) [27] and in these patients, confirmed sarcopaenia was defined as low ASM (i.e. <20 kg in males and <15 kg in females) [27].

Sarcopaenic obesity was defined using the two-step algorithm of the European Society for Clinical Nutrition and Metabolism (ESPEN) and European Association for the Study of Obesity (EASO) [26]. The screening cut-off was set at ≥30 kg/m^2 of body mass index (BMI). In screened patients, confirmed sarcopaenia considered both low handgrip strength (i.e. <26 kg in males and <16 kg in females) [27] and high relative FM (i.e. >27% FM in males and >38% FM in females) [28].

The level of physical activity was recorded using a Spanish-adapted scale based on World Health Organization questionnaires as follows [29]:

- High: ≥7 days of vigorous-intensity activities ($n = 2$, excluded from statistical analysis).
- Moderate: ≥7 days of any combination of walking, moderate- or vigorous-intensity activities.
- Light: ≥3 days of vigorous-intensity activities of at least 20 min per day or ≥5 days of moderate-intensity activities and/or walking of at least 30 min.
- Very light: No activity is reported or some activity is reported but not enough to meet the categories 'Light', 'Moderate' or 'High'.

Statistical analysis

Descriptive analysis

Statistical analysis was performed using R programming language v.4.3.1 (R core Team, Vienna, Austria) with RStudio v.2023.06.2 (Posit Software©, Boston, MA, USA) interface. Distribution shapes of continuous variables were assessed using histograms and Q-Q plots. Variables were presented using mean and standard deviation (SD) or median and quartiles (Q1–Q3) accordingly. Qualitative variables were presented using count and percentage.

Comparison of clinical data across CKD stages

Comparison of clinical data (i.e. handgrip and bioelectrical impedance) between CKD stages was performed using one-way ANOVA with Holm *post hoc* when normality and homoscedasticity assumptions (tested using Levene's test) were met. Otherwise, a Kruskal–Wallis test with a Wilcoxon rank sum *post hoc* test with a Holm correction was used. Effect size, calculated using *{effectsize}* package v.0.8.6, was reported using partial eta squared (η_p^2) or Cohen's d with pooled SD in multiple or binary comparisons, respectively. Effect sizes were considered as small ($\eta_p^2 \geq 0.01$, Cohen's d ≥ 0.2), medium ($\eta_p^2 \geq 0.06$, Cohen's d ≥ 0.5) or large ($\eta_p^2 \geq 0.14$, Cohen's d ≥ 0.8). Prevalence of sarcopaenia was tested across period of follow-up using the Cochran-Mantel-Haenzen for repeated measures and across CKD stages using the Chi-2 test (χ^2).

Mixed models

The effect of eGFR on the relationship between ASM and MVF was investigated using linear mixed models with *{nlme}* package v.3.1–162. MVF was considered as an outcome and ASM and

Table 1: Characteristics of patients across CKD stages.

		CKD groups			
	All	G1–G2	G3	G4	G5
N patients, *n* (% of total)	1098	67 (6.1)	314 (28.6)	390 (35.5)	327 (29.8)
Age (years), median (Q1–Q3)	65 (56–73)	61 (51–68)	66 (58–73)	66 (58–75)	63 (54–70)
Weight (kg), median (Q1–Q3)	69.1 (59.5–78.5)	65.0 (56.2–69.9)	68.3 (59.3–79.2)	69.3 (58.8–77.7)	71.0 (61.4–81.2)
Height (m), mean (SD)	1.59 (0.10)	1.56 (0.08)	1.58 (0.10)	1.58 (0.09)	1.60 (0.10)
BMI ($kg.m^2$), median (Q1–Q3)	27.3 (24.4–30.5)	26.1 (22.8–28.2)	27.6 (24.3–30.5)	27.3 (24.3–30.6)	27.3 (24.6–30.5)
Sex (females), *n* (%)	565 (51.5)	37 (55.2)	176 (56.1)	204 (52.3)	148 (45.3)
Education, *n* (%)					
Illiterate	22 (2.7)	1 (2.2)	13 (5.5)	5 (1.7)	3 (1.3)
Elementary school	228 (28.3)	5 (10.9)	52 (21.8)	102 (35.1)	69 (29.7)
Middle school	123 (15.2)	9 (19.6)	33 (13.9)	45 (15.5)	36 (15.5)
High school	395 (48.9)	29 (63.0)	125 (52.5)	126 (43.3)	115 (49.6)
University	39 (4.8)	2 (4.3)	15 (6.3)	13 (4.5)	9 (3.9)
CKD aetiology, *n* (%)					
Diabetes	320 (46.1)	16 (34.8)	78 (37.0)	117 (49.2)	109 (54.8)
Vascular	139 (20.0)	12 (26.1)	45 (21.3)	49 (20.6)	33 (16.6)
Glomerular	6 (0.9)	2 (4.3)	2 (0.9)	1 (0.4)	1 (0.5)
Immunologic	8 (1.2)	0	3 (1.4)	4 (1.7)	1 (0.5)
Other	60 (8.6)	1 (2.2)	25 (11.8)	21 (8.8)	13 (6.5)
Unknown	161 (23.2)	15 (32.6)	58 (27.5)	46 (19.3)	42 (21.1)
Physical activity level, *n* (%)					
Very light	259 (40.3)	13 (32.5)	69 (35.4)	99 (42.5)	78 (44.8)
Light	326 (50.8)	23 (57.5)	100 (51.3)	117 (50.2)	86 (49.4)
Moderate	55 (8.6)	4 (10.0)	25 (12.8)	16 (6.9)	10 (5.7)
High	2 (0.3)	0	1 (0.5)	1 (0.4)	0

eGFR as independent variables of interest. All the models were adjusted for age, sex, BMI, physical activity levels and CKD aetiology, and took into account patient's follow-up as a time effect (i.e. defined as a random slope) and individual baseline characteristics (i.e. defined as random intercept). A first model was built to assess the effect of independent variables only (Model 1); a second to consider a contrast approach between CKD stages so that any progressive impairment could be detected (Model 2); and a third to consider the interaction term between CKD stages and ASM (Model 3). Marginal (i.e. only fixed effects) and conditional (i.e. fixed and random effects) coefficients of determination for mixed models were calculated using *{MuMIn}* package v.1.47.5.

In keeping with common clinical practice, in mixed Models 1, eGFR was reversed in order to consider reduction in kidney function rather than an improvement (i.e. $-1 \times$ eGFR), stratified by intervals of 10 mL/min of eGFR.

Slope analysis

The slope analysis takes into account the slopes of MVF, ASM and eGFR over time (obtained from linear regressions), for each individual. The tripartite association was tested using regression models, considering MVF slope as a dependant variable, adjusted for sex and age, BMI and physical activity level at first visit.

Statistical significance was considered when *P*-values were <5%.

Ethical guidelines statement

The study was conducted in accordance with the Declaration of Helsinki. Since the study was not planned in advance, patients were not asked to give specific informed consent, and only generic consent for the use of anonymous data for research purposes was requested. The fact that the data were gathered without foreseeing a research goal attests to the fully independent nature of the evaluations.

RESULTS

Baseline data

The initial dataset of 5162 patients (Supplementary data, Table S1) had similar anthropometric characteristics to those of the final dataset ($n = 1098$; Table 1). Characteristics of patients across CKD stages are presented in Table 1. Overall, 75% of patients were >55 years old; 68.8% were overweight; the prevalence of males and females was balanced; and the physical activity level was reduced with CKD severity.

Muscle force across CKD stages

Muscle force and body composition were different in the early and late stages of CKD (Table 2). Absolute ASM was higher in the G5 group compared with the G4, G3 and G1–G2 groups ($P < .001$–.007, Cohen's $d = 0.331$–0.445). Relative ASM was higher in G5 compared with the G3 and G4 groups ($P < .001$, Cohen's $d = 0.287$–0.307). Absolute FM was higher in the G3 group compared with the G1–G2 and G5 groups ($P = .003$–.018, Cohen's $d = 0.226$–0.375). Relative FM was lower in the G5 group compared with the G4 and G3 groups ($P < .001$, Cohen's $d = 0.305$–0.440). Absolute MVF was lower in G4 compared with G5 ($P = .034$, Cohen's $d = 0.210$), while relative MVF_{ASM} was higher in G1–G2 compared with G4 and G5 ($P < .001$–0.003, Cohen's $d = 0.411$–0.576) and MVF_{ASM} in

Table 2: Body composition and handgrip results.

		CKD groups						
	All	G1–G2	G3	G4	G5	Test statistics	*P*-value	ES
Overall								
n (%)	1098	67 (6.1)	314 (28.6)	390 (35.5)	327 (29.8)			
ASM (kg), median (Q1–Q3)	17.8 (13.5–23.1)	16.2 (14.1–20.5)	17.1 (13.1–22.1)	16.7 (13.1–22.3)	19.5 (14.6–24.6)	$\chi^2(3) = 24.051$	<.001	0.022
ASM (%), median (Q1–Q3)	25.6 (20.9–31.0)	26.1 (21.6–31.4)	24.7 (20.5–30.3)	24.6 (20.2–30.1)	27.3 (22.5–32.1)	$\chi^2(3) = 21.255$	<.001	0.019
FM (kg), median (Q1–Q3)	24.2 (17.8–31.1)	21.3 (16.2–29.1)	25.7 (19.3–31.8)	25.0 (17.9–31.7)	22.6 (16.8–29.3)	$\chi^2(3) = 16.725$	.001	0.015
FM (%), median (Q1–Q3)	35.9 (27.8–44.2)	37.0 (26.4–43.9)	38.6 (30.4–46.5)	36.4 (28.7–44.7)	31.9 (25.6–40.9)	$\chi^2(3) = 33.697$	<.001	0.030
MVF (N), median (Q1–Q3)	206 (157–272)	220 (165–267)	206 (161–273)	196 (149–257)	220 (163–283)	$\chi^2(3) = 8.966$	.030	0.008
MVF_{ASM} (kg_{MVF}/kg_{ASM}), mean (SD)	1.24 (0.34)	1.36 (0.30)	1.31 (0.34)	1.22 (0.34)	1.18 (0.31)	$F(3,1094) = 12.050$	<.001	0.032
Males								
n (%)	533	30 (5.6)	138 (25.9)	186 (34.9)	176 (33.6)			
ASM (kg), median (Q1–Q3)	22.7 (19.4–26.4)	21.0 (17.6–23.9)	23.2 (19.8–26.2)	22.2 (18.0–26.1)	23.6 (20.1–27.4)	$\chi^2(3) = 10.873$	.012	0.020
ASM (%), median (Q1–Q3)	30.8 (27.9–34.0)	31.4 (29.0–34.5)	30.4 (27.5–33.5)	30.4 (27.6–33.9)	31.3 (28.5–34.3)	$\chi^2(3) = 5.793$	.122	0.011
FM (kg), median (Q1–Q3)	19.9 (15.2–26.0)	18.6 (14.4–23.1)	22.6 (17.2–28.2)	20.2 (14.6–26.1)	19.1 (14.7–24.8)	$\chi^2(3) = 9.925$	.019	0.019
FM (%), median (Q1–Q3)	28.5 (22.5–33.5)	26.3 (23.1–32.4)	30.5 (24.6–35.2)	28.7 (22.4–33.6)	27.1 (21.5–30.6)	$\chi^2(3) = 14.330$	.003	0.027
MVF (N), median (Q1–Q3)	270 (224–329)	272 (233–327)	292 (235–344)	254 (207–301)	272 (224–331)	$\chi^2(3) = 13.311$	.004	0.025
MVF_{ASM} (kg_{MVF}/kg_{ASM}), mean (SD)	1.25 (0.30)	1.39 (0.23)	1.33 (0.30)	1.22 (0.31)	1.20 (0.29)	$F(3,529) = 7.900$	<.001	0.043
Females								
n (%)	565	37 (6.5)	176 (31.2)	204 (36.1)	148 (26.2)			
ASM (kg), median (Q1–Q3)	14.0 (11.4–16.5)	14.4 (11.1–16.2)	13.8 (11.4–16.0)	13.5 (10.9–16.2)	14.6 (11.7–18.2)	$\chi^2(3) = 8.135$	.043	0.014
ASM (%), median (Q1–Q3)	21.1 (18.9–23.8)	22.1 (19.9–25.7)	20.8 (19.0–23.3)	20.6 (18.5–22.9)	21.9 (19.3–24.7)	$\chi^2(3) = 14.942$	.002	0.026
FM (kg), median (Q1–Q3)	27.9 (21.8–35.0)	25.6 (19.3–31.6)	27.8 (22.4–35.2)	28.8 (23.0–34.7)	26.7 (20.5–35.5)	$\chi^2(3) = 5.251$	.154	0.009
FM (%), median (Q1–Q3)	43.8 (37.9–48.2)	43.0 (37.4–46.8)	44.8 (40.0–48.7)	44.2 (39.8–48.4)	41.1 (35.8–46.7)	$\chi^2(3) = 16.676$	<.001	0.029
MVF (N), median (Q1–Q3)	164 (128–196)	175 (142–213)	168 (135–201)	156 (123–193)	165 (128–190)	$\chi^2(3) = 6.630$	.085	0.012
MVF_{ASM} (kg_{MVF}/kg_{ASM}), mean (SD)	1.24 (0.37)	1.33 (0.35)	1.30 (0.38)	1.22 (0.37)	1.16 (0.34)	$F(3,561) = 5.321$	.001	0.028

Statistics comprise F statistics in ANOVA or Kruskal–Wallis Chi-2 test (χ^2).
ES: effect size.

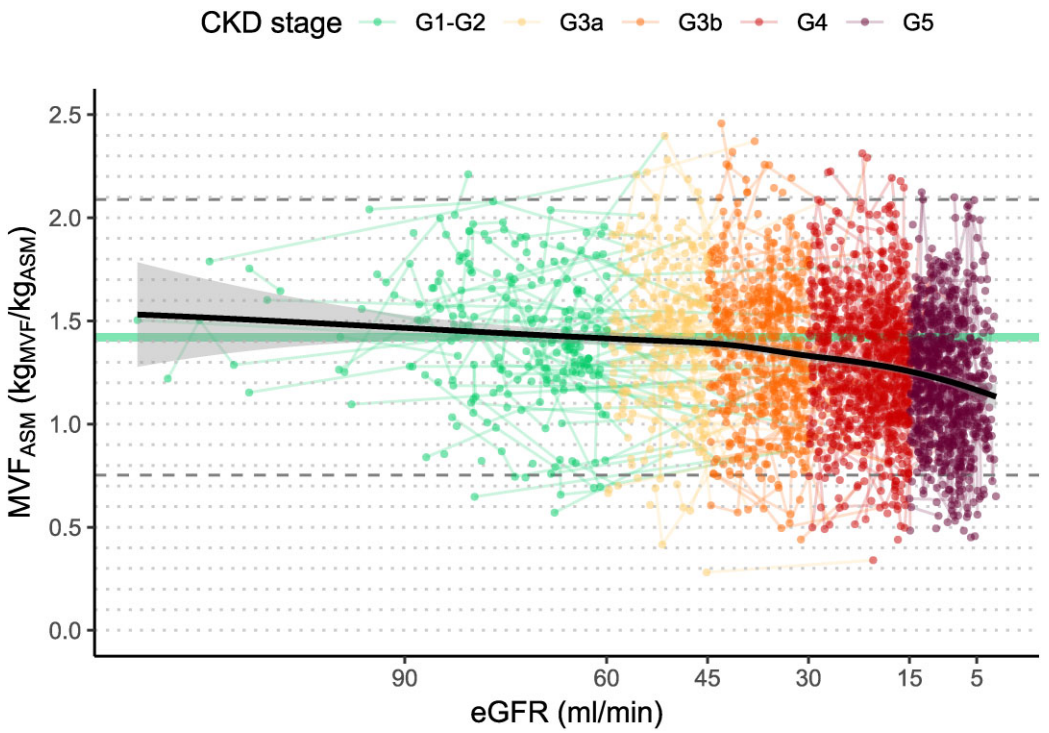


Figure 2: Relation between eGFR and MVF normalized for ASM mass (MVF_{ASM}), with longitudinal observations connected by lines. The green horizontal line and the grey dashed lines respectively represent the mean MVF_{ASM} of the G1–G2 group with the limits of agreement (±1.96 * SD); the solid black line represents the locally estimated scatterplot smoothing with the 95% confidence interval shown as the shaded grey area. a.u.: arbitrary unit.

Table 3: Handgrip prediction using a linear mixed model.

Unit: N		95% CI		
Fixed effect	Estimate	Lower	Higher	*P*-value
Model 1				
ASM (kg)	5.445	4.363	6.527	<.001
eGFR (per loss of 10 mL/min)	–2.805	–4.655	–0.956	.003
Model 2				
ASM (kg)	5.472	4.391	6.553	<.001
CKD stages (G1–G2)	Ref.			
G3	–1.492	–11.867	8.884	.780
G4	–8.539	–19.812	2.734	.141
G5	–16.859	–29.223	–4.495	.008
Model 3				
ASM (kg) × CKD stage G1–G2	Ref.			
ASM (kg) × CKD stage G3	–2.268	–3.927	–0.609	.008
ASM (kg) × CKD stage G4	–2.694	–4.593	–0.794	.006
ASM (kg) × CKD stage G5	–3.675	–5.626	–1.725	<.001

All models were adjusted for age, sex, BMI and physical activity level. Random slopes and intercepts were defined for time and individuals, respectively. Full models can be found in the Supplementary data, Table S2

Model 1: R^2 for fixed effects only (0.634) and with random effects (0.927); Model 2: R^2 for fixed effects only (0.635) and with random effects (0.927); Model 3: R^2 for fixed effects only (0.640) and with random effects (0.927).

G3 was also higher compared with G4 and G5 ($P < .001$–0.002, Cohen's d = 0.270–0.408). Despite being statistically significant in both sexes, MVF_{ASM} seems more impacted by CKD stage in males ($P < .001$, $\eta_p^2 = 0.043$) than females ($P = .001$, $\eta_p^2 = 0.028$).

As highlighted in Fig. 2, plotting all the observations of the final dataset, a reduction in MVF_{ASM} was first evident in CKD stage G3b and became more severe as CKD increased in severity.

Effect of CKD stage on the relationship between ASM and MVF

Independently of age, sex, BMI, physical activity levels and CKD aetiology, the relationship between MVF and ASM changes across CKD stages, as depicted in Table 3. For the sake of clarity, the predicted values of MVF according to observed ASM and

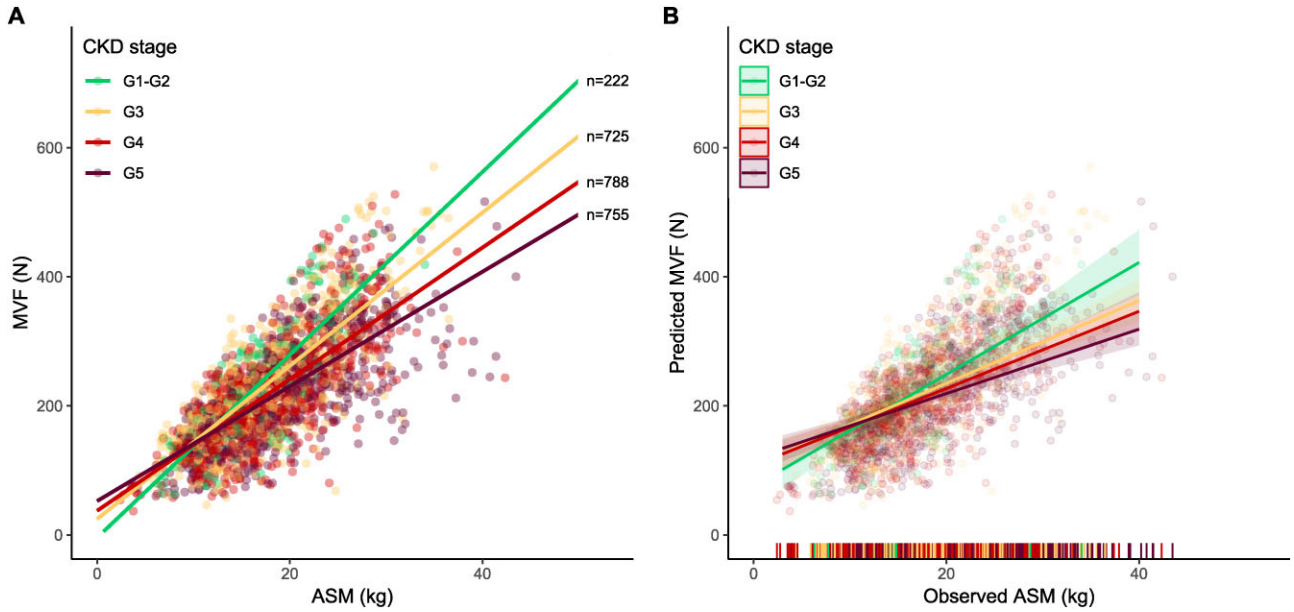


Figure 3: Relationship between (**A**) MVF and ASM with the linear fitting with respect to CKD group; and between (**B**) the predicted MVF derived from a mixed effects model (Model 3) and the observed ASM, with solid lines representing the statistical interaction terms according to CKD stage (Table 3).

the interaction terms shown in Model 3 were represented in Fig. 3B. Visually, differences in slope lead to differences in MVF starting from ~20 kg ASM, and are more evident in patients with higher ASM such as males compared with females (Supplementary data, Fig. S1).

Prevalence and evolution of sarcopaenia in CKD stages

Considering all CKD patients, the prevalence of confirmed sarcopaenia was quantified at 27.4% at their first consultation. Furthermore, 16.9% of patients were identified as with probable sarcopaenia (i.e. low muscle force only). Consequently, 44.3% of the CKD patients studied had suffered from low muscle force.

The prevalence of confirmed sarcopaenia was balanced across follow-up and CKD stages. The incidence of a new diagnosis of sarcopaenia during follow-up was similar in all CKD stages (Fig. 4A). Conversely, a shift from confirmed sarcopaenia to no sarcopaenia was observed in the early CKD stages, but was minimal in G4 and G5 (Fig. 4B).

Prevalence of sarcopaenic obesity in CKD stage

Of the 28.7% obese CKD patients at baseline, 10.5% were identified as having had confirmed sarcopaenic obesity (Fig. 4C). No difference in confirmed sarcopaenic obesity was noted during follow-up or across CKD stages at baseline.

The prevalence of sarcopaenic obesity remained stable during follow-up and across CKD stages (Fig. 4C and D). In this context, considering only obese patients (i.e. screened sarcopaenic obesity), the incidence of confirmed sarcopaenic obesity did not increase as CKD became more severe. On the contrary, recovery from sarcopaenic obesity (i.e. from confirmed sarcopaenic obesity to no sarcopaenic obesity) was noted in the G1–G2 group.

Slope analysis

Mean follow-up was 28.1 months. As shown in Supplementary data, Fig. S2, the relationship between eGFR and MVF slopes over time remained highly heterogeneous and no direct association was found in the regression analysis. Of note, MVF slopes were lower in males compared with females [–20.270 (95% confidence interval –39.431, –1.108) N/year, $P = .038$] and associated with ASM slopes [1.036 (95% confidence interval 0.161, 1.911) N/year, $P = .021$], adjusted for age, sex, BMI and physical activity levels. However, MVF slopes were associated with the interaction between eGFR and ASM slopes [0.078 (95% confidence interval 0.019, 0.136) N/year, $P = .010$], adjusted for age, sex, BMI and physical activity levels.

DISCUSSION

The present study demonstrated for the first time in humans that the relationship between muscle mass and muscle force production changes across CKD stages (Fig. 3, Table 3). The lower the eGFR, the lower the slope of the relation between MVF and ASM, i.e. for any given muscle mass, muscle force production decreases as CKD progresses.

The second important result, derived from the slope analysis, is that there is a negative independent association between MVF evolution over time and the interaction of eGFR and ASM evolution over time, further suggesting that CKD-related progressive impairment in muscle strength is related not just to changes in ASM.

The third important result was to describe that recovery from sarcopaenia or sarcopaenic obesity is possible. Recovery was most often observed in the early CKD stages. This emphasizes the importance of early CKD detection and suggests that the earlier treatment begins, the more likely it is to be effective.

It is well acknowledged that CKD patients have lower muscle force compared with matched peer controls [4, 30]. The odds of having low muscle force increases starting in CKD stage 2 compared with controls and stage 1 patients [21]. In a multiple

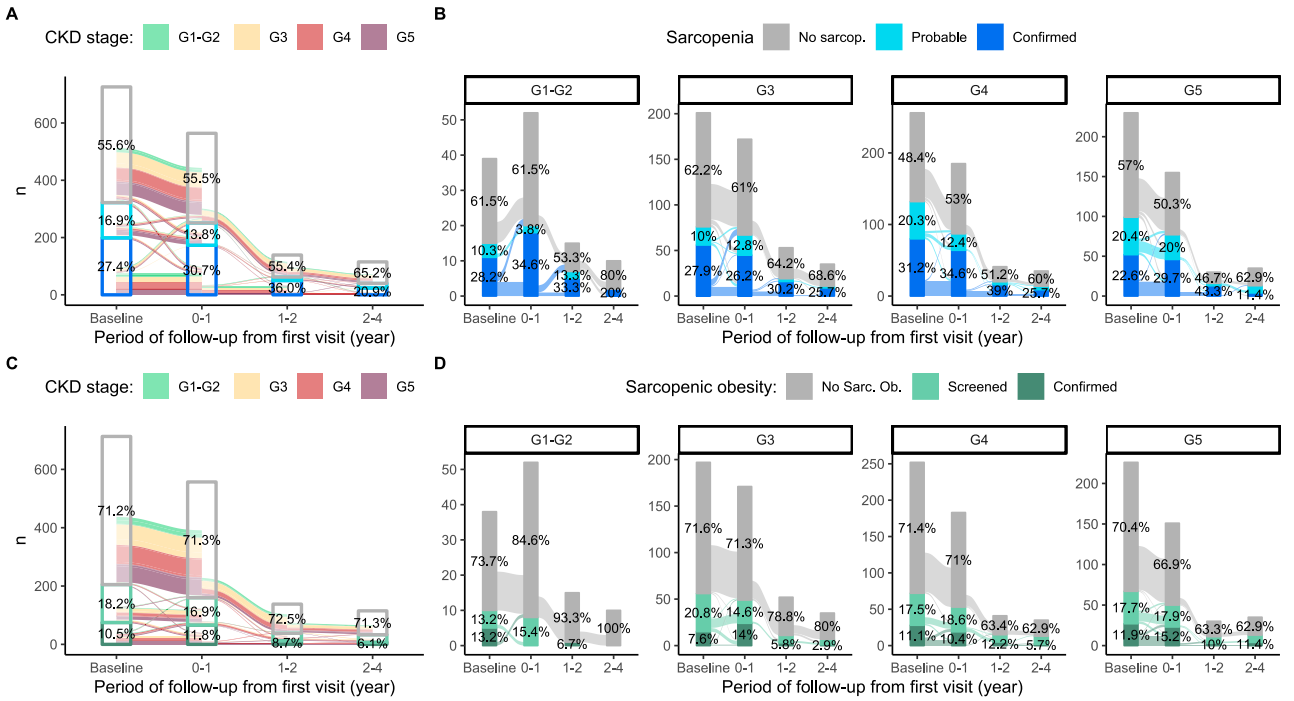


Figure 4: Prevalence of sarcopaenia as defined by EWGSOP-2 (**A**, **B**) and sarcopenic obesity as defined by ESPEN and EASO (**C**, **D**) during different periods of follow-up from baseline (connecting curves, called alluviums, represent individual evolutions in sarcopaenic status over time).

regression model adjusted for several cofounding factors, a significant association between eGFR and MVF was found [20]. Our results are in accordance, confirming this negative association (Table 3) but also identifying a precocious impairment in MVF_{ASM} associated with eGFR decline (Fig. 2, Table 3).

Of note, very few previous studies have reported longitudinal data on muscle mass and muscle force in CKD patients. In a 2-year longitudinal follow-up study, Leikis *et al.* (2006) found a stable thigh muscle cross-sectional area with a reduction of 10 mL/min/1.73 m^2 in eGFR (i.e. 35 to 25 mL/min/1.73 m^2), but a statistically significant reduction in leg MVF at most of the angular velocities tested [31]. A similar discrepancy between MVF and ASM in CKD was recently described in isolated muscle fibres of CKD mice. This impairment was associated with a reduction in myosin heads bound to actin [17]. Our results are in accordance with these murine models in showing a gradual impairment as CKD progresses in human. The impairment of force production in CKD is twofold: qualitative and severity-related. (i) Qualitative: the differences in slopes leading to different MVF were more marked in patients with higher ASM (evident starting at ~20 kg ASM); this suggests that results may be offset in patients with severe sarcopaenia, but also indicates that interventions to preserve force should be extended to include CKD patients with preserved muscle mass. (ii) Severity: the onset of impairment in force production appears to visually start from CKD G3b (Fig. 2). Tables 2 and 3 show a gradual reduction in MVF as eGFR decreases (Table 3, Model 2) although a significant difference only observed in G5 compared with G1–G2. The higher ASM and MVF in CKD stage 5 group may be due to the competitive mortality effect (i.e. the healthier stage 5 patients are enrolled). This counterintuitive finding needs to be confirmed in other longitudinal studies. Most importantly, the relationship between MVF and ASM is already reduced since CKD G3 compared with G1–G2, independently of age, sex, BMI, physical activity level and CKD aetiology. These important findings highlight the importance of therapies aimed at improving muscle function and quality (e.g. physical exercise) in addition to those focused on maintaining muscle mass (e.g. nutritional management).

It is noteworthy that the eGFR calculation used a creatinine-based equation, which potentially overestimates eGFR in individuals with low ASM [32]. This limitation could impact on the results. However, as the main findings of the study are especially pronounced in individuals with high ASM and the slopes between ASM and MVF across CKD stages were considered throughout the entire range of ASM, this may have a limited effect on the conclusions. The primary factors that have been considered to explain the loss of muscle force and mass include neurologic impairment [11–13], myosteatosis [14, 16], mitochondrial dysfunction and uraemic toxins [15], inflammation and hormonal imbalance [10], in addition to geriatric problems.

With regard to the longitudinal effect of CKD on MVF and ASM, our analysis showed that MVF evolution over time seems not exclusively associated with eGFR slopes but rather impacted by the interaction of eGFR and ASM slopes over time. Despite this finding, as shown in Supplementary data, Fig. S2, the dispersion of individual slopes suggests that several factors modulate this outcome at the individual level. Physical activity level was not associated with MVF evolution in this population, a finding probably explained by the non-interventional design of the study in an overall inactive cohort of CKD patients. Overall, the involvement of eGFR evolution on the association of ASM and MVF slopes over time in CKD patients points to the need to develop integrative therapeutics, i.e. considering as many neuromuscular function determinants as possible, rather than focusing on muscle mass only.

To contextualize the third relevant point, the worldwide prevalence of sarcopaenia in CKD patients was recently estimated at 20.4% [33]. In Mexico, the prevalence of sarcopaenia is

estimated at 33.3% in CKD patients, which is in keeping with our results [33]. An increase in the prevalence of sarcopaenia across CKD stages is a matter of debate [34]. Previous studies did not find statistically significant differences between CKD stages [33, 35, 36] or display conflicting results [37]. However, a recent study showed an association between sarcopaenia and rapid decline in kidney function [38]. Sarcopaenic obesity is associated with poorer health outcomes compared with sarcopaenia or obesity alone [39], but this is debated in CKD patients [40]. The prevalence of sarcopaenic obesity is estimated at 10%–12% in CKD patients [33], and varies widely depending on definition criteria. The prevalence of sarcopaenic obesity in our study is in line with the state of the art, ranging from 7.6% to 13.2%, and sarcopaenia and sarcopaenic obesity do not differ across CKD stages at baseline, as has been shown in other reports [33, 35, 36].

Our study is one of the few to add information obtained during follow-up; interestingly the incidence of new cases of confirmed sarcopaenia or sarcopaenic obesity was not different in CKD stages (Fig. 4) and recovery from both conditions was observed mainly in the early CKD stages. Although we cannot exclude a bias of inclusion of G1–G2 patients (where only proactive patients about healthcare were most likely observed in these centres), we hypothesize that this positive outcome is explained by nutritional, exercise or therapeutic actions allowing ASM, MVF or FM improvement.

Limitations

The large sample size is the most important strength, together with the fact that data were gathered 'blindly', i.e. before this study was planned, in the context of routine care. The cohort was almost exclusively composed of CKD patients from Mexico and our findings require confirmation in ethnically diverse populations. It is to be expected that patients followed up at CEAN centres have better nutritional status and therefore may not be fully representative of the Mexican CKD population. Physical activity levels were estimated using interviews and ASM using bioelectrical impedance. This latter evaluation can be affected by hydration status [41], which carries the risk of overestimating ASM in the late CKD stages [19], but remains reliable in CKD patients with normal hydration [42]. The handgrip task only involves the upper limbs, however it allows rapid muscle function assessment in daily clinical practice [3, 4] and is less sensitive to the cofounding effect of peripheral neuropathy, which commonly affects the lower limbs of CKD patients with or without diabetes [13].

The effect size of CKD on different markers may have been underestimated because the reference group was composed of CKD G1–G2 patients and they cannot be assimilated to non-CKD controls. However, this may even reinforce interest in the differences between CKD stages. Lack of biochemical data other than data on kidney function, data on body water and lack of comorbidity details (in addition to CKD aetiology) are a limit of the study and will be implemented in future research that will address also the relationship between muscle force and comorbidities. Finally, groups were defined using a creatinine-based equation, which may predispose to misclassification. However, quantification of serum cystatin-C is expensive, limiting its use especially in low- and middle-income countries.

CONCLUSIONS

eGFR decrease negatively affects the musculoskeletal system, leading to lower muscle force production for any given level of muscle mass. This reduction is more evident in patients with preserved muscle mass. Over time, a reduction in muscular force in CKD patients is independently associated with the interaction of eGFR and ASM reduction. While the prevalence of sarcopaenia and sarcopaenic obesity at baseline did not differ across CKD stages, recovery seems to be more frequent in the early CKD stages.

Our results highlight the importance of focusing on force determinants (e.g. myofibrillar protein function, neural activation, metabolic balance) in further research protocols in order to better delineate the CKD-related impairment of the neuromuscular function, at rest and during exercise. These results also reinforce the necessity of promoting and implementing physical exercise programs aimed at improving muscle function and quality, in addition to nutritional management. Rehabilitation programs should ideally start in the early CKD stages, and patients with preserved muscle mass should also be included in these programs, in order to improve or preserve musculoskeletal health, and consequently quality of life and survival in CKD patients.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

A.C. and G.B.P designed the study protocol. J.N.H., R.U.A. and A.G.E. gathered the data. A.C., G.B.P. and P.-Y.M. analysed the data. A.C. and P.-Y.M. drafted the tables and figures. A.C., G.B.P., P.-Y.M. and M.T. interpreted the data and drafted the manuscript. All authors reviewed and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The dataset employed and the R-script for statistical analysis can be found in the following repository (https://doi.org/10.17605/OSF.IO/BM9ZD).

CONFLICT OF INTEREST STATEMENT

A.C., M.T. and G.B.P. received consultancy fees from Fresenius Kabi Inc. for data cleaning and organization, but the funder was not involved, in whatever way, in the study design, conduction, data analysis or manuscript drafting. J.N.H., R.U.A. and A.G.E. work in the CEAN Centers.

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