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Dynapaenia and sarcopaenia in chronic haemodialysis patients: do muscle weakness and atrophy similarly influence poor outcome?

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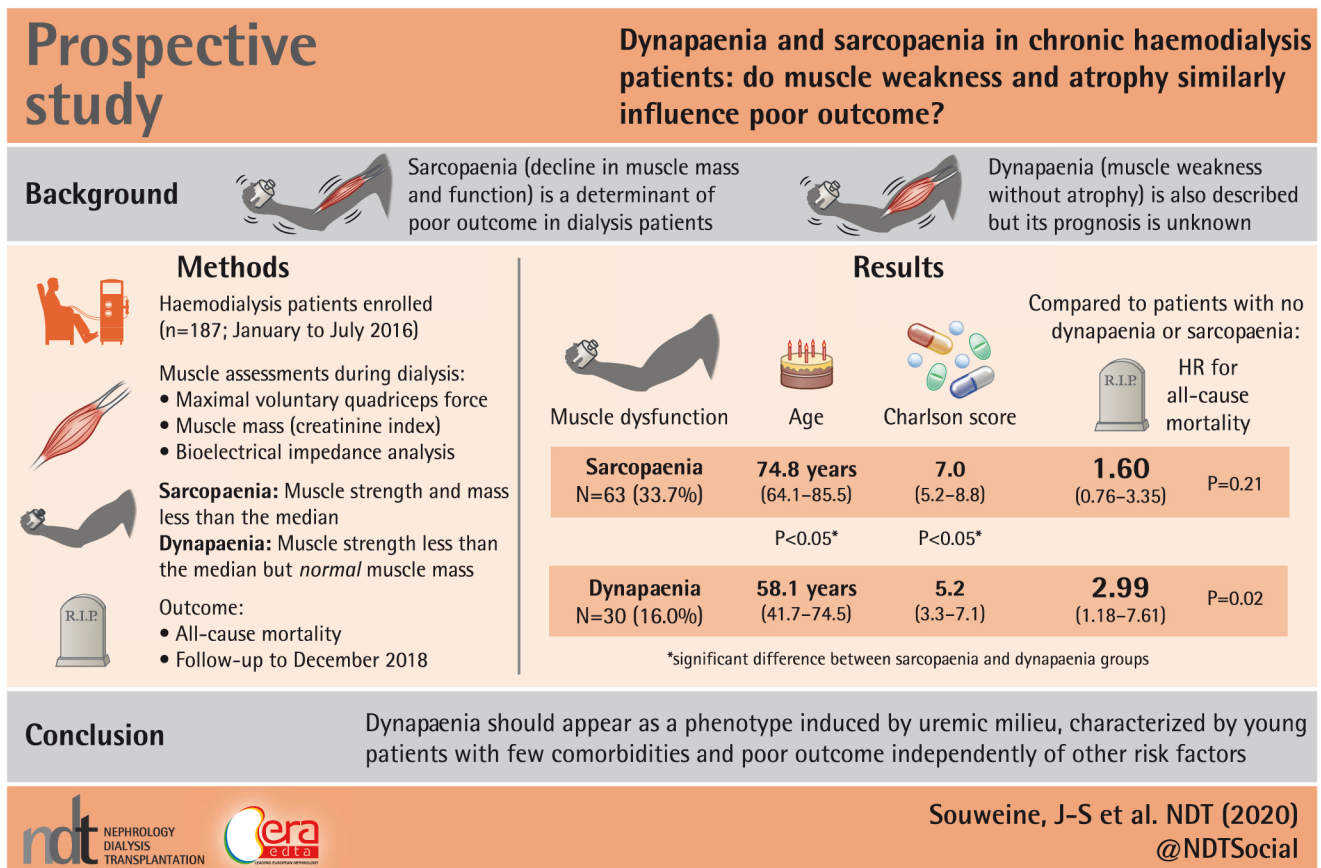
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**Clinical trial registration: NCT03845452

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GRAPHICAL ABSTRACT



Conclusion

Dynapaenia should appear as a phenotype induced by uremic milieu, characterized by young patients with few comorbidities and poor outcome independently of other risk factors




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What is already known about this subject?

- sarcopaenia defined as a decline in muscle mass and strength contributes to the frailty and emerges as an important risk factor of death in chronic haemodialysis (CHD) patients;
- dynapaenia, defined as a muscle weakness without a decrease in muscle mass, has been recently evidenced in CHD patients and confirms that muscle strength and muscle mass are not solely dependent on each other; and
- identification of dynapaenic in CHD patients may help defining a constitute disease phenotype as suggested in a recent cohort, and could partly explain why nutritional supplementation and rehabilitation had blunted effects in CHD patients. However, in CHD patients, the characteristics and clinical outcome of patients with dynapaenia remain unknown.

What this study adds?

- muscle function, assessed by muscle strength and physical activity, constitutes a better prognostic factor than muscle mass in CHD patients;
- dynapaenia was associated with a poor outcome after multivariate adjustment including age, whereas sarcopaenia did not remain statistically significant; and
- our findings highlighted the fundamental role of muscle function in comparison with muscle mass to predict mortality.

What impact this may have on practice or policy?

- first, our study highlights that screening for muscle dysfunction, such as weakness and physical inactivity and muscle mass assessment, is crucial to predict outcome of CHD patients. Indeed, assessing only muscle mass could blind the high risk of mortality associated with dynapaenia; and
- secondly, it suggests that identification of dynapaenia will help to propose a more targeted therapeutic intervention on muscle dysfunction and rehabilitation management with the eventual goal of improving dialysis patient outcomes as previously demonstrated in elderly patients. Finally, it can be hypothesized that muscle functional impairment is the consequence of structural abnormalities independently of muscle atrophy or ageing. Thus, muscle rehabilitation and physical exercise should be more suitable for patients with dynapaenia compared with a patient with sarcopaenia.

ABSTRACT

Background. Sarcopaenia, defined as a decline in both muscle mass and function, has been recognized as a major determinant of poor outcome in haemodialysis (HD) patients. It is generally assumed that sarcopaenia is driven by muscle atrophy related to protein-energy wasting. However, dynapaenia, defined as weakness without atrophy, has been characterized by a different disease phenotype from sarcopaenia. The aim of this study was to compare the characteristics and prognosis of sarcopaenic and dynapaenic patients among a prospective cohort of chronic HD (CHD) patients.

Methods. Two hundred and thirty-two CHD patients were enrolled from January to July 2016 and then followed prospectively until December 2018. At inclusion, weakness and atrophy were, respectively, evaluated by maximal voluntary force (MVF) and creatinine index (CI). Sarcopaenia was defined as the association of weakness and atrophy (MVF and CI below the median) while dynapaenia was defined as weakness not related to atrophy (MVF below the median, and CI above the median).

Results. From a total of 187 prevalent CHD patients [65% of men, age 65.3 (49.7–82.0) years], 44 died during the follow-

up period of 23.7 (12.4–34.9) months. Sarcopaenia and dynapaenia were observed in 33.7 and 16% of the patients, respectively. Compared with patients with sarcopaenia, patients with dynapaenia were younger and with a lower Charlson score. In contrast, mortality rate was similar in both groups (38 and 27%, respectively). After adjustment for age, sex, lean tissue index, serum albumin, high-sensitivity C-reactive protein (hs-CRP), haemoglobin (Hb), normalized protein catabolic rate (nPCR), dialysis vintage and Charlson score, only patients with dynapaenia were at increased risk of death [hazard ratio (HR) = 2.99, confidence interval 1.18–7.61; $P = 0.02$].

Conclusions. Screening for muscle functionality is highly warranted to identify patients with muscle functional impairment without muscle atrophy. In contrast to sarcopaenia, dynapaenia should appear as a phenotype induced by uraemic milieu, characterized by young patients with low Charlson score and poor prognosis outcome independently of serum albumin, hs-CRP, Hb, nPCR and dialysis vintage.

Keywords: chronic haemodialysis, dynapaenia, muscle mass, muscle strength, sarcopaenia

Sarcopaenia, defined as a decline in muscle mass and strength, is becoming a concerning challenge for chronic haemodialysis (CHD) patients [1, 2]. Patients with sarcopaenia present decreased physiological reserves and poor response to stressors, the main features of frailty condition [3]. Thus, sarcopaenia contributes to frailty and emerges as an important risk factor of death [4].

While muscle mass and strength are physiologically interrelated in healthy subjects and CHD patients, basic physiological studies only showed a mild correlation between muscle strength and mass, and muscle strength should therefore not be considered as a surrogate for muscle mass in healthy subjects [5]. Dynapaenia, defined as a muscle weakness without decrease in muscle mass, has been recently evidenced in CHD patients and confirms that both entities are not solely dependent on each other in these patients [6, 7]. Therefore, from a simple statistical point of view, a significant CHD patient cluster might experience muscle weakness without atrophy. In addition, the determinants of sarcopaenia do not impact muscle mass and strength similarly [8, 9]. While muscle mass mainly depends on malnutrition and chronic inflammation related to protein-energy wasting (PEW) [10–12], muscle strength has also been associated with other factors such as physical activity, neural activation and muscle contractile quality [13, 14].

Evidence of any distinction between dynapaenia and sarcopaenia in CHD patients should require different therapeutic strategies of muscle disorders such as those previously observed in elderly [7]. Thus, identification of dynapaenic CHD patients may help define a constitutive disease phenotype as suggested in a recent cohort [15], and could partly explain why nutritional supplementation and rehabilitation had blunted effects in CHD patients [16–19].

Yet, this muscle phenotype has never been identified, mainly because muscle strength remains poorly investigated in CHD patients. Only muscle mass is routinely investigated, either by bioelectrical impedance analysis (BIA) or by creatinine kinetic modelling [20–22]. However, weakness detection using a simple, inexpensive and reliable strain gauge could also be assessed in clinical practice [23]. Recently, it has been suggested that muscle strength *per se* was associated with poor clinical outcomes in CHD patients [24]. Defining a disease phenotype requires that patients of a same group share consistent clinical and physiological characteristic experiences and a consistent natural history (reflecting an underlying pathobiology and a predictable response to general and specific therapies) [25–27]. However, in CHD patients, the characteristics and clinical outcomes of patients with dynapaenia remain unknown. Indeed, it has never been demonstrated that such a group of dynapaenic CHD patients experiences a specific time course.

Therefore, the aim of this study was to compare the characteristics of sarcopaenic and dynapaenic patients among a prospective cohort of CHD patients. In addition, we aimed to test the association between muscle mass and function with mortality using readily applicable bedside tools, and the prognostic value of sarcopaenia and dynapaenia in a multivariate analysis.

Study design and patients

This is a *post hoc* cross-sectional analysis with prospective follow-up from an initial observational study investigating determinants of muscle weakness in prevalent CHD patients [6]. End-stage chronic renal disease patients, stable in HD for >3 months, were enrolled from January 2016 to July 2016 in HD units of Languedoc Roussillon, France (Lapeyronie University Hospital and centres issued from a non-profit dialysis association). Non-inclusion criteria were unstable comorbidities, acute illness for <3 months, cardiovascular contraindication to physical activity, and musculoskeletal or neurological disorders.

Ethics statement

The study was conducted according to the principles of the declaration of Helsinki and in compliance with International Conference on Harmonization/Good Clinical Practice regulations. The research protocol was initially approved by the local institutional ethics committee in January 2016 (with the following number: 2015-A01854-45) (ClinicalTrials.gov Identifier: NCT02806089) to investigate in a cross-sectional study the determinants of muscle weakness in prevalent CHD patients. A second approval has been further obtained in December 2018 (2018_IRB-MTP_12-02) (ClinicalTrials.gov Identifier: NCT03845452) to record mortality over a 2-year period.

Procedures

Clinical examination, biological parameters, muscle mass and strength measurements were performed during the same dialysis session on the day of inclusion. Patient characteristics including age, gender, treatment modalities, duration of kidney disease and dialysis vintage were reviewed. History of comorbidities was performed using Charlson score for each patient. Evaluation of routine biological parameters including urea, creatinine, serum high-sensitivity C-reactive protein (hs-CRP), serum albumin, bicarbonate and phosphates was carried out on an automated Cobas 8000 (Roche, Meylan, France). Dialysis adequacy was estimated by calculation of Daugirdas single pool (spK_t/V urea). Normalized protein catabolic rate (nPCR) was calculated from pre- and post-dialysis blood urea and dialysis adequacy [28, 29]. Patients were followed-up until December 2018 and mortality recorded. Follow-up time was censored at kidney transplantation, change of dialysis facility, lost to follow-up or end of study (December 2018).

Muscular parameter determination

Maximal voluntary force (MVF) of quadriceps and BIA were assessed during the same dialysis session.

Muscle mass was assessed by creatinine kinetic modelling using creatinine index (CI) and BIA using the body composition monitor (Fresenius Medical Care, Bad Homburg, Germany) [21, 30], with collection of lean tissue index (LTI) and fat tissue index (FTI). Muscle mass evaluation using BIA and CI was performed after the midweek HD session [21].

Voorrips score assessed physical activity and represented an integrative model of muscle function during the last 3 months before evaluation [31].

Assessment of quadriceps MVF was assessed using a hand-held dynamometer, as previously described [23].

Sarcopaenia and dynapaenia diagnosis

Sarcopaenia was defined as muscle strength and mass below the median of both MVF and CI. Dynapaenia was defined as the muscle strength below the median of MVF and a CI above the median value of CI (normal muscle mass).

Statistical analyses

Sample size was computed according to the method described in Latouche *et al.* [32] and implemented in the powerSurvEpi R package. In this context, sarcopaenia was considered as the bivariate covariate of interest. Assumptions needed for computation of sample size were based on the study of Isoyama *et al.* [15], as follows: prevalence of sarcopaenia in the study population = 21%; observed hazard ratio (HR) = 2.94; power ($1 - \beta$) = 80%; proportion of death during follow-up = 29%. This formula led to a sample size of 163. Considering 10% of patients lost to follow-up, the needed sample size was 180 patients.

Population characteristics were expressed as mean (mean $-$ 1 SD/mean $+$ 1 SD) for quantitative variables and as proportions for categorical variables. Logarithm transformations were performed for Voorrips score and hs-CRP data to obtain a normal sampling distribution. For quantitative data, multiple pairwise comparisons (Tukey test) were performed

after a significant global test (ANOVA test if ANOVA hypotheses were fulfilled, Kruskal–Wallis test if not). For categorical data, multiple pairwise comparisons with Bonferroni correction were performed after a significant global chi-squared test. Survival analysis was assessed using Cox proportional hazard model to test the association between muscle mass and function with mortality. All variables in univariate analysis were subsequently tested in multivariate analysis. A stepwise procedure using Akaike information criterion (AIC) was used to select potential variables in the final model. In addition, a Bayesian Information Criteria (BIC) was also tested (see [Supplementary data](#), S1) [33].

The Kaplan–Meier method of survival was used to assess the ability of dynapaenia and sarcopaenia to predict all-cause mortality in the population. Except parameters used to define sarcopaenia or dynapaenia and Voorrips score, which is a redundant variable with MVF to assess muscle function, all variables in univariate analysis were subsequently tested in multivariate analysis. Cox regression analyses are presented as HRs with 95% confidence intervals using a stepwise procedure. A test was considered significant at $P < 0.05$. Analyses were carried out using the R version 3.5.1 software.

RESULTS

Baseline characteristics of patients

One hundred and eighty-seven CHD patients [65% men, age 65.3 (49.7–82.0) years] were included in the study ([Figure 1](#)). Charlson score was 5.8 (3.6–8.1), spK_t/V urea

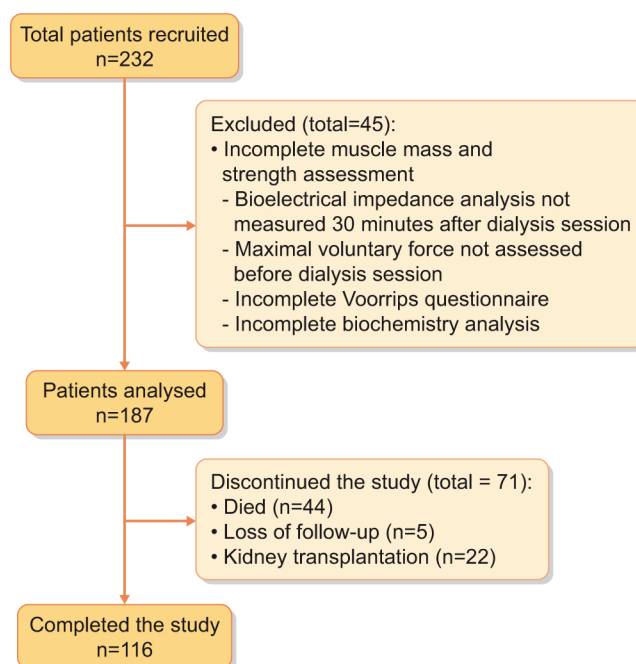


FIGURE 1: Flow chart diagram depicting number of patients evaluated for eligibility and number of patients included in analysis.

was 1.8 (1.4–2.1) and dialysis vintage was 5.6 (0–12.4) years (Table 1). Muscle parameters were as follows: CI 19.1 (16.4–21.7) mg/kg/day, LTI 11.9 (9.3–14.5) kg/m², MVF 88.1 (48.5–127.8) Nm. A low physical activity, assessed by a Voorrips score at 6.9 (1.1–12.8) was observed (Table 1).

Causes of end-stage renal disease were glomerulonephritis (13.9%), diabetes mellitus (15.5%), hypertensive nephrosclerosis (14.4%), intricate aetiology (diabetes and hypertension) (7.5%), other cause (32%) and undetermined nephropathy (16.0%). There was no difference between patients with sarcopaenia, dynapaenia and patients with no dynapaenia–no sarcopaenia concerning aetiology of chronic kidney disease (CKD).

Sarcopaenia was present in 33.7% while dynapaenia was observed in 16.0% of the patients (Figure 2). Muscle mass, MVF and physical activity estimated by Voorrips score significantly increased in patients with no dynapaenia–no sarcopaenia ($P < 0.05$ for all these comparisons). Body mass index (BMI), hs-CRP and haemoglobin (Hb) were not significantly different in patients with sarcopaenia, dynapaenia and no dynapaenia–no sarcopaenia. Compared with sarcopaenic patients, patients with dynapaenia were younger and had few comorbidities ($P < 0.05$). Finally, no significant difference in Voorrips score between dynapaenia and sarcopaenia groups was observed.

Mortality

Forty-four patients died within a mean follow-up period of 23.7 (16.8–34.3) months, 12 (13%) in the no sarcopaenia–no dynapaenia group, 8 (27%) in the dynapaenia group and 24 (38%) in the sarcopaenia group. In the sarcopaenia group,

mortality rate was more important compared with the no dynapaenia–no sarcopaenia group. Main causes of death were cardiovascular ($n = 13$; 30%), infection ($n = 11$; 25%), cancer ($n = 7$; 16%), other ($n = 8$; 18%) and unknown ($n = 5$; 11%). Concerning aetiology of death, no difference between all groups was found (Table 2).

Muscle parameters and mortality rate

Results from the Cox proportional hazard analyses exploring the predictive value for mortality of muscle parameters are reported in Table 3. Low CI, muscle strength and physical activity were risk factors for mortality in unadjusted analyses (respectively: HR = 0.79, 95% confidence interval 0.69–0.9; $P < 0.001$, HR = 0.98, 95% confidence interval 0.97–0.99; $P < 0.0001$, HR = 0.13, 95% confidence interval 0.05–0.33; $P < 0.001$). Only a non-significant trend was observed with LTI in the univariate analysis (HR = 0.89, 95% confidence interval 0.79–1.00; $P = 0.057$).

In order to identify whether muscle mass, MVF or physical activity were independently associated with mortality, these parameters were introduced into a multivariate model using a stepwise procedure. MVF, Voorrips score and Hb but not CI remained statistically significant (HR = 0.99, 95% confidence interval 0.98–1.00; $P = 0.015$, HR = 0.28, 95% confidence interval 0.11–0.72; $P = 0.008$, HR = 0.76, 95% confidence interval 0.60–0.97; $P = 0.028$, respectively).

Table 1. Characteristics of the CKD patients according to presence or absence of muscle dysfunction

Parameters	Total population <i>n</i> = 187	No dynapaenia–no sarcopaenia <i>n</i> = 94	Dynapaenia <i>n</i> = 30	Sarcopaenia <i>n</i> = 63
Demographic and clinical characteristics				
Age, years	65.3 (49.7–82.0)	62.1 (45.6–78.6) ^s	58.1 (41.7–74.5) ^s	74.8 (64.1–85.5) ^{n, d}
Gender, men, <i>n</i> (%)	122 (65)	77 (82) ^s	18 (60)	27 (43) ⁿ
<i>spK_v/V</i>	1.8 (1.4–2.1)	1.6 (1.3–2.0) ^s	1.8 (1.5–2.0)	1.9 (1.6–2.2) ⁿ
Charlson score	5.8 (3.6–8.1)	5.2 (2.8–7.6) ^s	5.2 (3.3–7.1) ^s	7.0 (5.2–8.8) ^{n, d}
Duration of CKD, years	13.6 (2.1–25.2)	13.8 (2.6–25.1)	16.4 (1.7–31.1)	12.1 (1.9–22.3)
Dialysis vintage, years	5.6 (0–12.4)	5.3 (0–11.7)	8.3 (0–18.0)	4.9 (0–10.3)
BMI, kg/m ²	24.8 (20.0–29.7)	25.0 (21.2–28.8)	24.5 (19.2–29.7)	24.7 (18.7–30.6)
Pre-dialysis systolic BP, mmHg	132 (107–158)	138 (113–162) ^s	138 (113–164) ^s	121 (96–146) ^{n, d}
Pre-dialysis diastolic BP, mmHg	65 (48–81)	69 (51–86) ^s	66 (53–80) ^s	57 (43–70) ^{n, d}
Voorrips score	6.9 (1.1–12.8)	8.7 (2.1–15.3) ^{d, s}	5.7 (0–11.7) ⁿ	4.9 (1.3–8.4) ⁿ
MVF, Nm	88.1 (48.5–127.8)	119.4 (89.0–149.7) ^{d, s}	59.0 (43.3–74.7) ⁿ	55.4 (40.0–70.8) ⁿ
Impedancemetry parameters				
FTI, kg/m ²	12.7 (6.8–18.6)	11.9 (7.2–16.7)	13.1 (7.3–19.0)	13.6 (6.3–21.0)
LTI, kg/m ²	11.9 (9.3–14.5)	13.0 (10.6–15.4) ^{d, s}	11.4 (9.3–13.5) ^{n, s}	10.5 (8.2–12.8) ^{n, d}
SMMI, kg	7.7 (6.3–9.1)	8.4 (7.1–9.6) ^{d, s}	7.6 (6.5–8.7) ^{n, s}	6.9 (5.6–8.2) ^{n, d}
Laboratory parameters				
CI, mg/kg/day	19.1 (16.4–21.7)	20.2 (17.6–22.8) ^s	20.6 (19.3–21.9) ^s	16.8 (15.4–18.3) ^{n, d}
Serum albumin, g/L	38.0 (33.5–42.5)	38.9 (34.3–43.6) ^s	37.3 (33.1–41.6)	36.9 (32.8–40.9) ⁿ
hs-CRP, mg/L	10.2 (0–28.8)	9.6 (0–27.6)	14.2 (0–42.1)	9.3 (0–23.0)
nPCR, g/kg/day	0.91 (0.68–1.14)	0.93 (0.70–1.15)	0.97 (0.72–1.23)	0.86 (0.64–1.08)
Serum bicarbonate, mmol/L	22.5 (19.9–25.2)	22.5 (19.9–25.0)	21.6 (19.4–23.8) ^s	23.0 (20.2–25.9) ^d
Serum phosphate, mmol/L	1.44 (0.93–1.96)	1.51 (0.97–2.05) ^s	1.63 (1.15–2.11) ^s	1.26 (0.82–1.7) ^{n, d}
Hb, g/dL	11.1 (9.7–12.5)	11.1 (9.6–12.5)	11.4 (10.1–12.7)	11.1 (9.7–12.4)

Results are expressed as mean (mean – 1 SD; mean + 1 SD). *n* = significant difference with 'No dynapaenia–no sarcopaenia' group ($P < 0.05$). *d* = significant difference with dynapaenia group ($P < 0.05$). *s* = significant difference with sarcopaenia group ($P < 0.05$).

SMMI, skeletal muscle mass index.

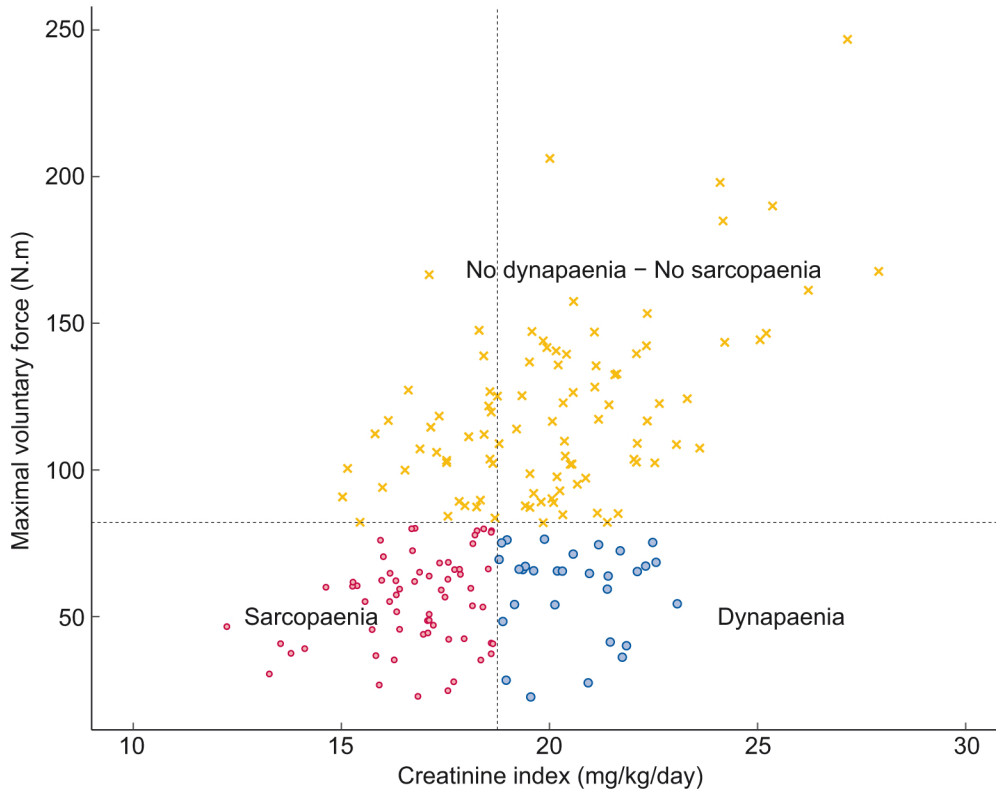


FIGURE 2: The distribution of CHD patients according to CI and MVF. Lines indicate the median of CI and MVF for the detection of sarcopaenia, dynapaenia and no dynapaenia–no sarcopaenia.

Table 2. Aetiology of death during the follow-up

Characteristic	Total population <i>n</i> = 187	No dynapaenia–no sarcopaenia <i>n</i> = 94	Dynapaenia <i>n</i> = 30	Sarcopaenia <i>n</i> = 63
Mortality, <i>n</i> (%)	44(23)	12 (13) ^s	8 (27)	24 (38) ⁿ
Main causes of death				
Cardiovascular	13	4	1	8
Cancer	7	2	2	3
Infection	11	4	2	5
Others	8	1	3	4
Unknown	5	1	0	4

n = significant difference with 'no dynapaenia–no sarcopaenia' group ($P < 0.0001$). *s* = significant difference with sarcopaenia group ($P < 0.0001$).

Sarcopaenia/dynapaenia and mortality rate

Kaplan–Meier method including sarcopaenia and dynapaenia versus no dynapaenia–no sarcopaenia is shown in [Figure 3](#) and Cox proportional hazard models using dynapaenia or sarcopaenia are shown in [Table 4](#).

Patients with no dynapaenia–no sarcopaenia were considered as the reference group. In the univariate analysis, Cox proportional hazard analyses showed that sarcopaenia was associated with a higher mortality risk ($P = 0.002$) and dynapaenia tended to be significant ($P = 0.08$). In order to identify whether sarcopaenia or dynapaenia were independently associated with mortality, all variables in the univariate analysis were subsequently introduced into a multivariate model using a step-wise procedure. In multivariate analysis, only dynapaenia but not sarcopaenia was associated with higher mortality risk (HR = 2.99, 95% confidence interval 1.18–7.61; $P = 0.02$,

HR = 1.60, 95% confidence interval 0.76–3.35; $P = 0.21$, respectively).

DISCUSSION

The main finding of our work underlines that muscle strength and physical activity constitute a better prognostic factor than muscle mass in CHD patients. Indeed, dynapaenia was associated with a poor outcome after multivariate adjustment including age, whereas sarcopaenia did not remain statistically significant. Thus, weakness was associated with mortality independently of muscle mass and age in dynapaenia group, although the mean age difference was ~20 years between dynapaenic and sarcopaenic groups, suggesting an important role of muscle quality in CHD.

Table 3. Cox proportional hazards analysis of factors predicting all-cause mortality

Parameters	Unadjusted Cox proportional hazard			Multivariate Cox proportional analysis		
	HR	95% confidence interval	P-value	HR	95% confidence interval	P-value
Age, years	1.05	(1.03–1.08)	<0.001	1.04	(1.01–1.06)	0.011
Gender (men versus women)	0.75	(0.41–1.38)	0.35	–	–	–
LTI, kg/m ²	0.89	(0.79–1.00)	0.057	–	–	–
CI, mg/kg/day	0.79	(0.69–0.9)	<0.001	–	–	–
MVF, Nm	0.98	(0.97–0.99)	<0.001	0.99	(0.98–1.00)	0.015
Voorrips score	0.13	(0.05–0.33)	<0.001	0.28	(0.11–0.72)	0.008
Serum albumin, g/L	0.88	(0.83–0.94)	<0.001	–	–	–
hs-CRP, mg/L	1.16	(0.63–2.13)	0.64	–	–	–
Hb, g/dL	0.79	(0.63–0.99)	0.04	0.76	(0.60–0.97)	0.028
nPCR, g/kg/day	0.23	(0.05–1.02)	0.052	–	–	–
Charlson score	1.32	(1.17–1.48)	<0.001	–	–	–
Dialysis vintage, years	1.00	(0.95–1.04)	0.9	–	–	–
spK _t /V	0.77	(0.31–1.9)	0.57	0.42	(0.18–0.99)	0.048

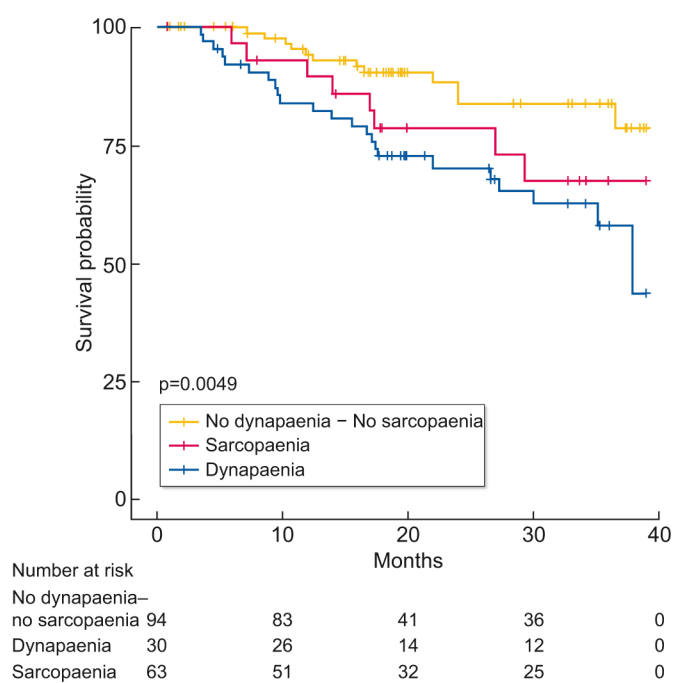


FIGURE 3: Kaplan–Meier curve for survival free from no dynapaenia–no sarcopaenia, dynapaenia and sarcopaenia among CHD patients.

Exploring muscle function beyond muscle mass

Muscle mass is recognized as an important predictor of mortality in CHD patients [21, 22, 30]. In the dialysis population, muscle mass could be assessed by different methods including DEXA, impedancemetry or creatinine kinetic modelling. DEXA is recognized as the gold standard to evaluate body composition and muscle mass, but because it is costly, time-consuming and not a portable technique it is not appropriate for daily practice. Thus, it has been recommended to use BIA at the bedside, which is a simple, non-invasive and inexpensive method well correlated with DEXA measurements [20]. CI, influenced by low protein dietary intake, was performed on the

midweek HD session as recommended by experts [30]. Interestingly, we confirmed in our study the negative correlation between CI and mortality in the univariate analysis. In addition, the CI threshold value for mortality was at 18.8 mg/kg/day, which is close to the one published in previous studies (18.9 mg/kg/day) [21, 22, 30]. However, this association between muscle mass and mortality does not reach significance in the multivariate analysis (Table 3). This unexpected result may be explained by the strong association between muscle function (Voorrips score and MVF) and mortality in the multivariate analysis, highlighting the importance of a global screening of muscle function with specific values in HD population.

Table 4. Risk factors of mortality in unadjusted and adjusted after AIC stepwise analysis including dynapaenia and sarcopaenia groups

Parameters	Unadjusted Cox proportional hazard		Multivariate Cox proportional analysis	
	HR (95% confidence interval)	P-value	HR (95% confidence interval)	P-value
No dynapaenia–no sarcopaenia	Reference		Reference	
Dynapaenia	2.2 (0.9–5.4)	0.084	2.99 (1.18–7.61)	0.02
Sarcopaenia	3.0 (1.5–6.0)	0.002	1.60 (0.76–3.35)	0.21
Age, years	1.05 (1.03–1.08)	<0.001	1.03 (0.99–1.07)	0.13
Gender (men versus women)	0.75 (0.41–1.38)	0.35	–	–
LTI, kg/m ²	0.89 (0.79–1.00)	0.057	–	–
Serum albumin, g/L	0.88 (0.83–0.94)	<0.001	0.93 (0.87–1.05)	0.086
hs-CRP, mg/L	1.16 (0.63–2.13)	0.64	–	–
Hb, g/dL	0.79 (0.63–0.99)	0.04	0.82 (0.63–1.05)	0.11
nPCR, g/kg/day	0.23 (0.05–1.02)	0.052	–	–
Charlson score	1.32 (1.17–1.48)	<0.001	1.21 (1.00–1.46)	0.049
Dialysis vintage, years	1.00 (0.95–1.04)	0.9	–	–
<i>spK_v/V</i>	0.77 (0.31–1.9)	0.57	–	–

In CHD patients, no *a priori* specific and validated cut-off value exists to identify muscle mass and strength diminution. Reference values are speculated using reference values from older patients without CKD or low muscle mass and strength of CHD patients are defined against young reference populations [1, 15, 24]. This methodology leads to results that are sometimes difficult to interpret. Nevertheless, assessment of MVF of quadriceps, using a handheld dynamometer, has been recently validated against the gold standard (dynamometer chair) [23]. This reliable tool presents many advantages: (i) it can be used at the bedside and (ii) a handheld dynamometer limits measurement biases, compared with handgrip, because it is not influenced by local disorders such as arteriovenous fistula [1, 23, 24]. Voorrips score also assesses muscle function using an integrative model of physical activity in the last 3 months before muscular evaluations [34]. Interestingly, muscle strength and physical activity are closely linked ($r = 0.39$, $P < 0.001$). Although our results demonstrate the importance of physical activity and muscle strength, we could not currently affirm the implication of the unloading and deconditioning in muscle abnormalities of CHD patients.

Outcome is mainly driven by uraemia-induced muscle dysfunction and dynapaenia

Table 3 demonstrates in multivariate analysis that muscle function assessed by muscle strength and physical activity, but not muscle mass, is associated with poor outcome. This result is in agreement with previous reports in the general population or in HD [15, 24, 35]. Indeed, in incident [15] and prevalent [24] dialysis patients, low muscle strength was more strongly associated with mortality than low muscle mass.

The key role of muscle function and muscle strength is further enhanced by the relationship between dynapaenia and mortality. Indeed, dynapaenia was associated with a poor

outcome after multivariate adjustment including age, sex, LTI, serum albumin, hs-CRP, serum bicarbonates, dialysis vintage and Charlson score, whereas sarcopaenia did not remain statistically significant (Table 4).

In the general population, dynapaenia is related to age-related decline in muscle strength [36], and muscle strength decline is greater in men than women. In contrast to the first studies in CHD patients showing similarities with age-related sarcopaenia [18, 37, 38] (fibre atrophy, activation of ubiquitin–proteasome catabolic pathway, etc.), older age was not a significant determinant of poor prognosis in multivariate analysis. This result is in line with recent studies showing that muscle remodelling in CHD patients and its underlying proteome is disease-specific [39] and not an accelerated ageing process. In particular, the fibre transition from slow-to-fast type reported in CHD patients [39–43] was the opposite of what is basically observed in ageing [44]. In addition, muscle atrophy is a relatively small contributor to the loss of muscle strength in older people especially in CHD patients [6, 45, 46]. As previously reported [15], gender was not associated with prognosis in multivariate analysis despite a different sex ratio between groups. Thus in CKD, behind the age-related decline in muscle mass, muscle function alteration was driven by many other factors such as uraemic toxins [47].

Thus, weakness was associated with mortality independently of muscle mass and age in dynapaenia group. This result highlights the role of muscle quality in CHD outcome and suggested that dynapaenia could appear as a muscular phenotype in CHD patients.

Is dynapaenia a muscular phenotype in CHD patients?

Dynapaenic and sarcopaenic CHD patients presented different clinical and biological characteristics (Table 1). Since dynapaenic patients were younger with few comorbidities, it could

be hypothesized that dynapaenic patients are pre-sarcopaenic patients and that these two groups correspond to the same patients taken at a different time point of the disease course. Indeed, an experimental study has demonstrated that muscle weakness appeared at an earlier stage of renal failure than muscle atrophy [48]. However, two results argue against this hypothesis of an historical continuum from one cluster to another. First, younger dynapaenic CHD patients were characterized by worse acidosis, phosphate levels and blood pressure (BP), which are classical indicators of CKD severity, than older sarcopaenic patients (Table 1). Classically, acidosis was strongly correlated with decreased kidney function [49] and could stimulate myostatin and muscle atrophy [50]. Serum bicarbonates are significantly increased in the sarcopaenic group in comparison with dynapaenic group, but not with the no sarcopaenic–no dynapaenic group. In CHD, nutrition and low protein intake should be taken into account in the interpretation of serum bicarbonates [51, 52]. Interestingly, albumin decreased in sarcopaenic patients but not in dynapaenic ones, suggesting a role of nutrition in age-related decline in muscle strength in sarcopaenic group.

The relationship between serum phosphates and muscle function remains a question of debate and could be modified by nutritional factors, bone and mineral disorders, inflammation, etc. Chen *et al.* first suggested that phosphate level was associated with low muscle strength [53]. In agreement with the recent report of MONDO (MONitoring Dialysis Outcome initiative), we observed a weak positive correlation between serum phosphate and MVF ($r = 0.19$, $P = 0.016$) [54]. Secondly, younger dynapaenic CHD patients did not have a better prognosis than older and comorbid sarcopaenic patients (Table 2). Thus, dynapaenic patients had a specific time course of the disease independently of age or comorbidities.

Given the accepted definition of a disease phenotype, patients with dynapaenia or sarcopaenia could constitute different phenotypes [25, 26]. When comparing our patient groups, they shared specific clinical characteristics, natural history and specific prognosis (Tables 1 and 2). As reported in Table 2, the mortality rate increased from the no dynapaenia–no sarcopaenia group (13%) to the dynapaenia group (27%) and the sarcopaenia group (38%). Although not statistically different, more deaths seemed to occur in sarcopaenic patients who were older than dynapaenic ones. More events were also registered in dynapaenic patients in comparison with the no sarcopaenia–no dynapaenia group, despite a similar mean age. We can hypothesize that in older sarcopaenic patients, death was probably strongly driven by age and comorbidities, whereas muscular quality was a determinant in younger HD patients. Because different prognosis factors have been previously identified in large CHD patients cohorts, the possibility of phenotypes in CHD patients has been proposed [40, 41]. Yet, our study is the first one to show that a dynapaenic phenotype in HD is associated with a high mortality rate despite young age, low Charlson score and metabolic acidosis, and a maintained systolic BP.

The link between disease phenotype and muscle functional impairment has not been currently characterized. Muscle biopsy studies in CHD patients have shown (i) a switch in the

muscular fibre phenotype from Types I to II [42, 55, 56], (ii) a fibre atrophy [57] and (iii) a mitochondrial dysfunction [58]. Thus, sarcopaenic CHD patients may experience a fibre atrophy while dynapaenic patients may rather experience an oxidative switch [39, 58, 59]. In addition, specific mechanisms could specifically lead to muscle weakness without atrophy, like architecture and neuromuscular transmission [60, 61]. The relative contribution of age, uraemic milieu and PEW in these phenotypes remains to be investigated. Altogether, future cellular muscle studies should characterize the phenotype (i.e. dynapaenic or sarcopaenic) of CHD patients.

Clinical relevance

This study has important implications for clinical practice and future research. First, it highlights that screening for muscle dysfunction, such as weakness, physical inactivity and muscle mass assessment, is crucial to predict outcome of CHD patients. Indeed, assessing only muscle mass with creatinine modelling or BIA could blind the high risk of mortality associated with dynapaenia. Secondly, it suggests that the identification of dynapaenia will help to propose a more targeted therapeutic intervention on muscle dysfunction and rehabilitation management with the eventual goal of improving dialysis patient outcomes, as previously demonstrated in elderly patients [7]. Finally, it can be hypothesized that muscle functional impairment is the consequence of structural abnormalities independently of muscle atrophy or ageing. Thus, muscle rehabilitation and physical exercise should be more suitable for patients with dynapaenia compared with patients with sarcopaenia.

Study limitations

This study had some limitations. The sample size was relatively low in this monocentric study. Model selection of variables associated with outcome remains crucial [33]. Some authors recommended BIC as a pertinent statistical method for model selection. Since BIC penalizes complex models, with a high number of parameters, it could be concluded that, besides a potential masking effect of comorbidities and albumin, dynapaenia weighted more than sarcopaenia in both AIC and BIC models. Nonetheless, our main objective, which was to compare the characteristics and outcomes of dynapaenic or sarcopaenic patients, has been achieved. In addition, the stability of these phenotypes should be confirmed in other CHD populations. However, these results may encourage future studies to evaluate structural muscle abnormalities and their causal effects in functional impairment leading to different muscle phenotypes in CHD patients.

CONCLUSION

In conclusion, screening for muscle functionality is highly warranted to identify patients with muscle functional impairment without muscle atrophy. Dynapaenia might appear as a phenotype induced by uraemic milieu, characterized by young patients with few comorbidities and poor prognosis outcome independently of other adjustment factors. Conversely, sarcopaenia should be mainly associated with ageing and comorbidities in CHD patients. Thus, the research focus should

be to improve muscle function and to investigate the impact of rehabilitation strategy upon the different phenotypes of CHD patients according to their distinctive muscle characteristics.

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AUTHORS' CONTRIBUTIONS

Conceptualization by J.-S.S., M.H., F.G. and J.-P.C. Data curation was done by A.R. Formal analysis was done G.P. and N.K. Funding acquisition by J.-S.S. and J.-P.C. Investigation and methodology by J.-S.S., G.P., E.B. and F.R. Project administration was carried out by J.-P.C. Resources by L.C., L.P., N.R., I.O. and M.L.Q. Software by G.P., A.R. and N.K. Supervision, validation and visualization were done by E.B., F.R., M.H., M.L.Q., F.G. and J.-P.C. Writing the original draft, and review and editing were by J.-S.S., M.M., M.L.Q., J.M., M.H., F.G. and J.-P.C.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflict of interest.

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