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ORIGINAL ARTICLE

Beyond sarcopenia: frailty in chronic haemodialysis patients

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ABSTRACT

Background. Frailty, characterized by vulnerability, reduced reserves and increased susceptibility to severe events, is a significant concern in chronic haemodialysis (HD) patients. Sarcopenia, corresponding to the progressive loss of muscle mass and strength, may contribute to frailty by reducing functional capacity, mobility and autonomy. However, consensus lacks on the optimal bedside frailty index for chronic HD patients. This study investigated the influence of frailty on chronic HD patient survival and explored the associated factors.

Methods. A total of 135 patients were enrolled from January to April 2019 and then followed up prospectively until April 2022. At inclusion, frailty was assessed by the Timed Up and Go (TUG) and Short Physical Performance Battery (SPPB) tests including gait speed, standing balance and lower limb muscle strength.

Results. From a total of 114 prevalent chronic HD patients (66% men, age 67.6 ± 15.1 years), 30 died during the follow-up period of 23.7 months (range 16.8–34.3). Deceased patients were older, had more comorbidities and a higher sarcopenia prevalence ($P < .05$). The TUG and SPPB test scores were significantly reduced in patients who had died [SPPB total score: 7.2 ± 3.3 versus 9.4 ± 2.5; TUG time 8.7 ± 5.8 versus 13.8 ± 10.5 ($P < .05$)]. Multivariate analysis showed that a higher SPPB score (total value >9) was associated with a lower mortality risk [hazard ratio 0.83 (95% confidence interval 0.74–0.92); $P < .03$). Each component of the SPPB test was also associated with mortality in univariate analysis, but only the SPPB balance test remained protective against mortality in multivariate analysis. Older age, lower handgrip strength and lower protein catabolic rate were associated with SPPB total scores <9, SPPB balance score and TUG time >10 s.

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Conclusions. Screening for frailty is crucial in chronic HD patients, and incorporating SPPB, especially the balance test, provides valuable insights. Diminished muscle strength and inadequate protein intake negatively influence the SPPB score and balance in chronic HD patients. Effective identification and management of frailty can therefore improve outcomes.
CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov. NCT03845452.

Keywords: chronic haemodialysis, frailty, muscle mass, muscle strength, sarcopenia

KEY LEARNING POINTS

What was known:

- The impact of frailty on the survival of chronic haemodialysis (HD) patients is of concern due to the lack of optimal measures.
- The Timed Up and Go and Short Physical Performance Battery tests show promise in evaluating functional performance, including muscle-related factors.
- Previous research links frailty to mortality, but specific insights in chronic HD patients are limited.

This study adds:

- Frailty impacted 36–40% of chronic HD patients (TUG or SPPB).
- The total SPPB score correlated with mortality risk.
- Muscle weakness and malnutrition were key frailty determinants.
- Balance emerged as a protective factor, influenced by muscle strength and protein intake in chronic HD patients.

Potential impact:

- The study underscores frailty's prevalence in chronic HD patients and its link to higher mortality risk.
- The SPPB and TUG tests are valuable for assessing frailty, with the SPPB offering comprehensive insights through balance assessment.
- Addressing balance disturbances and fall risk is crucial in chronic HD patients.

INTRODUCTION

Despite significant advances in the treatment of chronic kidney disease (CKD), the mortality rate remains high among haemodialysis (HD) patients, emphasizing the importance of considering their health status, especially in older individuals with multiple health conditions [1]. While frailty and sarcopenia are interconnected, they represent distinct clinical entities. Frailty is a broader state of decreased resilience and increased vulnerability to stressors, potentially due to multiple causes including sarcopenia, which specifically denotes the loss of muscle mass and strength [2]. Frailty, a complex state of vulnerability, significantly impacts on the health and well-being of individuals and emerges as an objective indicator of adverse clinical events. It is characterized by a reduced physiological reserve and an increased susceptibility to adverse clinical outcomes [3]. In recent years there has been a growing recognition of frailty syndrome, particularly in the aging population and among HD patients [4–6], with clinical indicators encompassing unintentional weight loss, exhaustion, reduced physical activity capacity and slow walking speed. However, to date, no consensus on the most suitable measure of frailty in HD patients exists [7]. While the Fried frailty criteria have been validated, there is a need for a readily applicable bedside measure that adequately captures the complexity of frailty [8]. To address this gap, the Timed Up and Go (TUG) and Short Physical Performance Battery (SPPB) tests have shown promise as well-established clinical tests to assess functional performances in older adults and potentially in HD patients. The TUG test involves a timed movement sequence encompassing rising, walking and turning, serving as a basic mobility measure. Conversely, the SPPB test provides a summary score of balance, walking speed and chair stand performance [9]. However, despite the potential relevance of frailty in HD patients, the impact of frailty on mortality remains largely unknown and only a few studies have assessed the ability of SPPB and TUG to predict outcomes in these patients.

Sarcopenia, distinct but often coexisting with frailty, is defined as the progressive loss of muscle mass and strength associated with reduced physical activity, and it constitutes a fundamental component of the frailty syndrome [2]. Indeed, sarcopenia plays a pivotal role in diminishing functional capacity, contributing to the onset of frailty, and potentially leading to premature mortality [10, 11]. In HD patients, previous studies have associated sarcopenia, assessed by parameters such as the creatinine index, with poor outcomes [12, 13]. Furthermore, weakness and dynapenia (loss of muscle strength without the requirement of muscle mass reduction) have emerged as prognostic factors in this population [14, 15]. This suggests a potential association between muscle dysfunction and the development of frailty, as previously reported in elderly patients [16]. However, limited information exists regarding the prevalence of frailty among HD patients and its interrelationship with muscle dysfunction.

Thus the present study aims to assess the impact of frailty, as assessed by the SPPB and TUG tests, on the survival of long-term HD patients. Additionally, a secondary objective is to examine the clinical and biological factors that contribute to frailty, including sarcopenia, in order to improve our understanding of how these factors influence patient outcomes.

MATERIALS AND METHODS

Study design

This is a cross-sectional analysis with prospective follow-up in prevalent HD patients. Participants were enrolled from January to April 2019. They were followed up until April 2022 and the

mortality was recorded. Follow-up time was censored at kidney transplantation, change of dialysis facility, lost to follow-up or the end of the study (April 2022).

Patients

End-stage chronic renal disease patients, stable on HD for >3 months, were enrolled. Patients with unstable comorbidities; acute illness for <3 months, including recent hospitalizations (e.g. due to a severe infection), exacerbations of a chronic disease (such as an acute flare-up of chronic obstructive pulmonary disease), recent cardiovascular events (like myocardial infarction), major recent surgeries and severe acute infections (such as pneumonia); cardiovascular contraindications to physical activity and musculoskeletal or neurological disorders were excluded. Patients with any measurement bias in muscle mass or strength evaluations were also excluded from the analysis.

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 approved by the local institutional ethics committee in December 2018 (2018_IRB-MTP_12-02) (ClinicalTrials.gov identifier: NCT03845452).

Procedures

Clinical examination, biological parameters and muscle mass and strength measurements were performed during the same midweek HD session on the day of inclusion to ascertain their predictive value for mortality. Patient characteristics, including age, gender, treatment modalities, duration of kidney disease and dialysis vintage, were recorded. Comorbidities were evaluated using the Charlson comorbidity index (CCI) for each patient. Routine biological parameters, including urea, creatinine, high-sensitivity C-reactive protein (hs-CRP), serum albumin, bicarbonate and phosphates, were assessed using an automated Cobas 8000 system (Roche Diagnostics, Indianapolis, IN, USA). Dialysis adequacy was determined using the Daugirdas single-pool Kt/V_{urea} ($spKt/V_{urea}$) calculation and β_2-microglobulin determination. The normalized protein catabolic rate (nPCR) was calculated using pre- and post-dialysis blood urea and dialysis adequacy values. The protein energy wasting (PEW) score was calculated using the following criteria: serum immune turbidimetric albumin <35 g/l, body mass index (BMI) <23 kg/m^2, creatinine index <18.82 mg/kg/day and low dietary protein intake estimated by nPCR <1.0 g/kg/day [17–19].

Frailty diagnosis

The frailty diagnosis involved the use of two tests, the SPPB and the TUG test. The SPPB is composed of three timed parts: gait speed, standing balance and lower limb muscle strength. A score of 0–4 was assigned to each item, for a total score of 12 points. Low physical performance was indicated by an SPPB score <9 [8]. Gait speed was measured as the time taken to walk 3 m at a normal pace. Standing balance was assessed in three positions held for 10 s if possible. Muscle strength in the lower limbs was evaluated through a timed sit-to-stand action, performed repeatedly five times with arms held over the chest.

In the TUG test, participants were asked to stand up from a chair, walk and cross a 3-m mark on the floor with a normal pace, turn, walk back to the chair and sit down [20]. Timing began when the participant's back left the back of the chair and stopped when their buttocks touched the seat again. A TUG score of ≥10 s was used to indicate poor functional performance.

Muscular parameter determination

Maximal voluntary force (MVF) and muscle mass were assessed during the same dialysis session. Muscle strength was evaluated before a dialysis session using a Jamar handgrip dynamometer and chair stand test.

Muscle mass was performed after the midweek HD session and was assessed by creatinine kinetic modelling using the creatinine index and by bioelectrical impedance analysis (BIA) using the body composition monitor (Fresenius Medical Care, Bad Homburg, Germany) with collection of the lean tissue index (LTI) and fat tissue index (FTI) [21]. The creatinine index, which corresponds to the normalized creatinine production rate and being easily estimated using pre-dialysis creatinine values and Kt/V, was calculated to estimate body composition [12].

Sarcopenia is defined as low muscle strength and low muscle mass according to the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) [10]. The cut-off points used to define low muscle strength and low muscle mass were a chair stand test >15 s for five rises in the SPPB test and a creatinine index <18.82 mg/kg/day [6, 10, 15].

Statistical analyses

Population characteristics

Population characteristics were expressed as median [interquartile range (IQR)] for quantitative variables and as proportions for categorical variables. Log transformations were performed for hs-CRP data to obtain a normal sampling distribution. Comparisons were performed using the Mann–Whitney–Wilcoxon test for quantitative data and Fisher's exact test for categorical data.

Outcomes

Receiver operating characteristics (ROC) curves and area under the curve (AUC) were calculated to predict mortality for TUG time and SPPB total score using the pROC R package (R Foundation for Statistical Computing, Vienna, Austria). The correlation between TUG time and SPPB total score was performed with the Pearson coefficient. The Kaplan–Meier method of survival was used to assess the ability of TUG time or SPPB total score to predict all-cause mortality. Survival analysis was assessed using a Cox proportional hazards model to test the association between frailty and mortality. All variables (with $P < .05$) in the univariate analysis were subsequently introduced into a multivariate model. Except parameters used to define sarcopenia, which is a redundant variable, all variables in the univariate analysis were subsequently tested in the multivariate analysis. Cox regression analyses are presented as hazard ratios (HRs) with 95% confidence intervals (CIs) using a stepwise procedure. A test was considered significant at $P < .05$.

Linear regressions were used to further identify the determinants of TUG time, SPPB total score and balance score. Results were expressed as β coefficients (95% CI). Variables significant at the $\alpha = 0.05$ level in the univariate analysis were subsequently tested in the multivariate analysis. A stepwise procedure using the Akaike information criterion (AIC) was

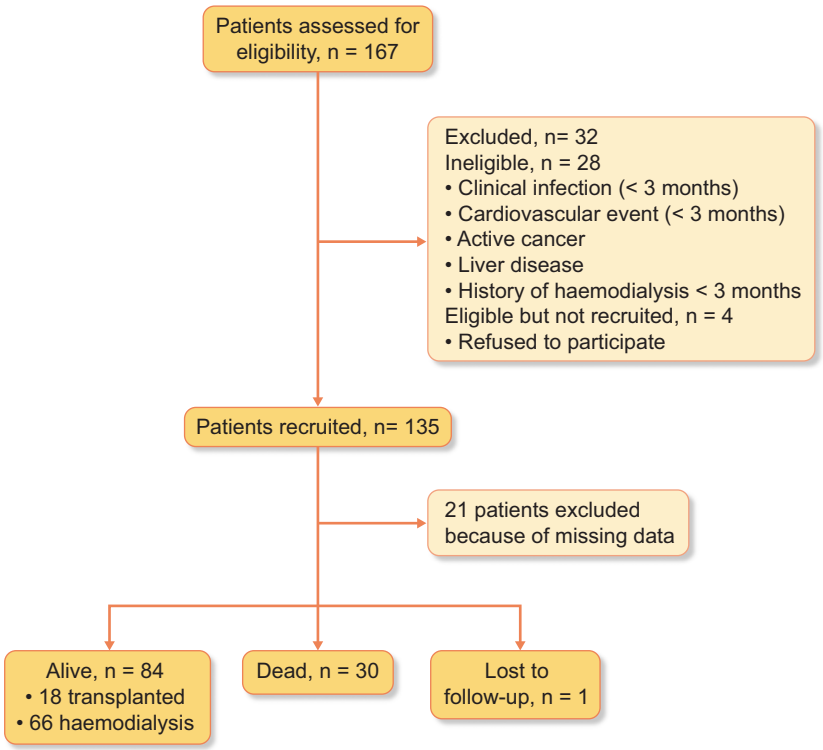

Figure 1: Flow chart depicting number of patients evaluated for eligibility and number of patients included in the analysis.

used to select potential variables in the final model. Analyses were carried out using R version 4.2.0 software (R Foundation for Statistical Computing).

RESULTS

Baseline characteristics of the patients

A total of 114 HD patients [66% men, age 70.3 years (IQR 18.6)] were included in the study (Fig. 1). The CCI was 6 (IQR 5), spKt/V_{urea} was 1.89 (IQR 0.39) and dialysis vintage was 5.0 years (IQR 11.93) (Table 1). Muscle parameters were as follows: creatinine index 19.0 mg/kg/day (IQR 3.9), LTI 11.4 kg/m^2 (IQR 4.5) and MVF 25.6 kg (IQR 16.2). Sarcopenia was present in 28% of the patients.

HD patients had a TUG performance of 7.6 s (IQR 6.5) and scored an SPPB median of 10 (IQR 4) and 40% and 64% of the patients were classified as frail according to SPPB and TUG classifications, respectively.

Follow-up of patients

Thirty patients died during a median follow-up period of 18.3 months (IQR 11.3). The main causes of death were as follows: cardiovascular [n = 6 (20%)], infection [n = 5 (17%)], cancer [n = 6 (20%)], other [n = 6 (20%)] and unknown [n = 7 (23%)]. Eighteen patients (15%) underwent transplantation during the study and were censored at the time of transplantation. The characteristics of transplant and non-transplant patients at the day of inclusion are given in Supplementary Table S1.

Comparison of alive and deceased patients at inclusion

As reported in Table 1, deceased patients were older and presented more comorbidities ($P < .05$) than living patients at inclusion. They also exhibited a lower MVF ($P < .05$), a lower creatinine index ($P < .05$) and an increase in the time required to complete the chair stand test ($P < .05$). The presence of PEW and sarcopenia was lower in the surviving patient group ($P < .05$). BMI, haemoglobin, dialysis vintage and aetiology of CKD were not significantly different between the groups.

The TUG test was significantly increased while SPPB was significantly decreased in deceased patients ($P < .05$) (Table 1). In the ROC analysis, the performances of the TUG or SPPB tests to predict mortality were 0.74 and 0.70, respectively (Supplementary Data, Figure S1a). A negative correlation between SPPB total score and TUG time was also observed ($r = -0.072$, $P < .001$) (Supplementary Data, Figure S1b).

Frailty as a determinant of mortality

The associations between mortality and SPPB total score or TUG time are presented in Fig. 2. Cox proportional hazards models using these functional performance measures are shown in Table 2. In the univariate analysis, high creatinine index, muscle strength and chair stand test were associated with a protective effect on mortality [HR 0.81 (95% CI 0.68–0.96), HR 0.96 (95% CI 0.92–0.99), HR 0.70 (95% CI 0.52–0.94), respectively]. In contrast, sarcopenia was associated with an increased mortality risk [HR 2.42 (95% CI 1.18–4.96)], while LTI did not reach significance in the univariate analysis [HR 0.92 (95% CI 0.81–1.05)]. Moreover, Cox proportional hazards analyses demonstrated that an increase in TUG time (measured in seconds) and a decrease in

Table 1: Patient characteristics based on their status at the end of the study follow-up: alive or dead.

Parameters	Total population ($n = 114$)	Alive ($n = 84$)	Dead ($n = 30$)	P-value
Demographic and clinical characteristics				
Age (years)	70.3 (18.6)	65.8 (16.4)	76.8 (9.4)	**<.001**
Male, *n* (%)	75 (66)	56 (67)	19 (63)	.74
Diabetes mellitus, *n* (%)	39 (34)	24 (29)	15 (50)	**.03**
CCI	6 (4.25)	5 (3.75)	9 (1.5)	**<.001**
spKt/V	1.89 (0.39)	1.86 (0.40)	1.95 (0.39)	.48
Dialysis vintage (years)	5.0 (12.0)	4.5 (13.2)	5.1 (9.7)	.34
BMI (kg/m^2)	25.4 (6.7)	25.5 (6.5)	24.1 (6.4)	.63
Pre-dialysis systolic BP (mmHg)	132 (27)	134 (27)	130 (28)	.40
Pre-dialysis diastolic BP (mmHg)	65 (25)	68 (25)	62 (27)	.07
MVF handgrip (Nm)	25.6 (16.2)	26.9 (14.7)	22.0 (12.0)	**.01**
Sarcopenia (creatinine index and SPPB chair), *n* (%)	32 (28)	18 (21)	14 (47)	**.008**
PEW, *n* (%)	19 (17)	7 (8)	12 (40)	**<.001**
TUG test (s)	7.6 (6.5)	7.0 (5.0)	10.8 (7.4)	**.001**
TUG >10 s, *n* (%)	41 (36)	23 (27)	18 (60)	**.001**
SPPB score	10 (4)	10 (3)	7 (4.75)	**<.001**
SPPB score <9, *n* (%)	46 (40)	28 (33)	18 (60)	**.01**
SPPB balance	4 (1)	4 (1)	3 (1.75)	**<.001**
SPPB chair	2 (2)	2.5 (3)	1.5 (1)	**.009**
SPPB gait speed	4 (1.0)	4 (0)	4 (2)	**.009**
Impedancemetry parameters				
FTI (kg/m^2)	13.4 (7.8)	12.9 (7.6)	14.0 (7.9)	.51
LTI (kg/m^2)	11.4 (4.5)	12.0 (4.1)	9.8 (3.8)	.09
Laboratory parameters				
Creatinine index (mg/kg/day)	19.0 (3.9)	19.3 (4.0)	17.7 (3.0)	**.005**
Serum albumin (g/l)	39.0 (6.1)	39.7 (5.2)	36.7 (6.8)	**.02**
hs-CRP (mg/l)	4.0 (8.9)	3.9 (8.8)	4.8 (9.9)	.38
nPCR (g/kg/day)	0.98 (0.28)	1.00 (0.26)	0.90 (0.29)	**.03**
Serum phosphate (mmol/l)	1.39 (0.81)	1.43 (0.79)	1.33 (0.86)	.48
Serum bicarbonate (mmol/l)	22.0 (2.6)	22.0 (2.9)	23.1 (2.2)	**.04**
Haemoglobin (g/dl)	11.7 (1.6)	11.6 (1.7)	11.8 (1.3)	.71
β_2-microglobin before	27.7 (11.1)	27.7 (10.5)	27.4 (11.7)	.48
β_2-microglobin after	6.5 (5.5)	6.9 (5.5)	5.9 (3.5)	.48
Change in β_2-microglobin before–after	20.1 (8.2)	19.6 (7.7)	20.7 (6.3)	.21

Values are presented as median (IQR) unless stated otherwise.

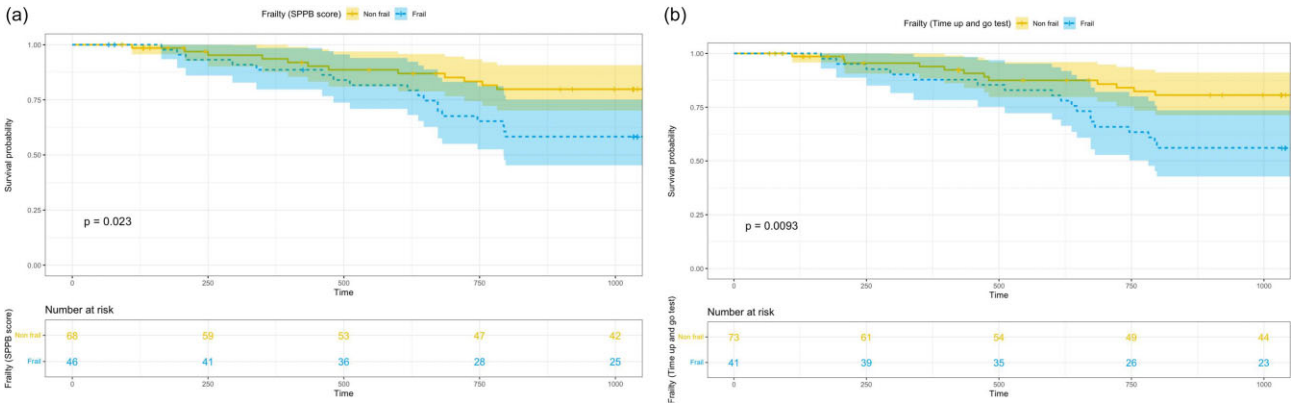

Figure 2: Kaplan–Meier mortality-free survival curve according to the **(a)** SPPB total score and **(b)** TUG test among HD patients. Low physical performance (frail patient) is indicated by an SPPB score <9 or TUG >10 s, whereas a non-frail patient has an SPPB score ≥9 or TUG ≤10 s.

the SPPB total score were associated with a higher mortality risk ($P < .0001$). In the multivariate analysis, a higher SPPB total score was associated with a lower mortality risk [HR 0.85 (95% CI 0.74–0.97); $P < .02$], whereas the duration of TUG time did not show a significant association with mortality risk.

In order to further analyse the relationships between SPPB components and mortality, we separately considered each domain. All three components (gait speed, standing balance and lower limb muscle strength) were individually associated with mortality in the univariate analysis. However, in the Cox

Table 2: Cox proportional hazards analysis of factors predicting all-cause mortality ($n = 114$).

	Unadjusted Cox proportional hazards			Multivariate Cox proportional hazards (with SPPB score)			Multivariate Cox proportional hazard (with the 3 tests included in the SPPB score)		
Parameters	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (years)	1.05	1.02–1.09	.001						
Male, *n* (%)	0.89	0.42–1.87	.76						
Diabetes mellitus, *n* (%)	2.11	1.03–4.32	.04						
CCI	1.4	1.2–1.63	<.001	1.35	1.16–1.58	<.001	1.35	1.15–1.58	<.01
spKt/V	1.08	0.37–3.09	.89						
Dialysis vintage (years)	0.99	0.96–1.03	.79						
BMI (kg/m^2)	0.97	0.91–1.05	.46						
Pre-dialysis systolic BP (mmHg)	0.99	0.98–1.01	.28						
Pre-dialysis diastolic BP (mmHg)	0.98	0.96–1.00	.07						
MVF handgrip (Nm)	0.96	0.92–0.99	.048						
Sarcopenia, *n* (%)	2.42	1.18–4.96	.016						
TUG test (s)	1.06	1.03–1.10	<.001						
SPPB score	0.83	0.74–0.92	<.001	0.85	0.75–0.97	.02			
SPPB balance	0.56	0.42–0.75	<.001				0.64	0.46–0.88	.007
SPPB chair	0.70	0.52–0.94	.02						
SPPB gait speed	0.69	0.52–0.92	.01						
FTI (kg/m^2)	1.01	0.96–1.07	.74						
LTI (kg/m^2)	0.92	0.81–1.05	.21						
Creatinine index (mg/kg/day)	0.81	0.68–0.96	.02						
Serum albumin (g/l)	0.92	0.85–0.99	.04						
hs-CRP (mg/l)	1.15	0.57–2.29	.70						
nPCR (g/kg/day)	0.15	0.02–0.92	.04	0.25	0.04–1.62	.15			
Serum phosphate (mmol/l)	0.76	0.35–1.64	.48						
Serum bicarbonate (mmol/l)	1.13	0.97–1.32	.13						
Haemoglobin (g/dl)	1.03	0.79–1.34	.84						

Table 3: Univariate analysis of variables associated with the SPPB score ($n = 114$).

	Unadjusted linear regression analysis			Multivariate linear regression analysis		
Parameters	Coefficient	95% CI	*P*-value	Coefficient	95% CI	*P*-value
Age (years)	−0.07	−0.11 to −0.04	**<.001**	−0.05	−0.09 to −0.02	**.001**
Gender	0.29	−0.83–1.41	.61			
CCI	−0.31	−0.51 to −0.12	**.002**			
Diabetes mellitus	−0.17	−1.29–0.94	.76			
spKt/V	−1.06	−2.64–0.52	.19			
Dialysis vintage (years)	−0.04	−0.09–0.02	.18			
BMI (kg/m^2)	−0.06	−0.16–0.04	.27			
Pre-dialysis systolic BP (mmHg)	0.01	−0.01–0.04	.29			
Pre-dialysis diastolic BP (mmHg)	0.05	0.02–0.07	**.001**			
MVF handgrip (Nm)	0.13	0.08–0.18	**<.001**	0.11	0.06–0.16	**<.001**
Sarcopenia	−3.34	−4.34 to −2.33	**<.001**			
FTI (kg/m^2)	−0.87	−0.95 to −0.79	**.04**			
LTI (kg/m^2)	0.18	0.02–0.35	**.03**			
Creatinine index (mg/kg/day)	0.45	0.25–0.66	**<.001**			
Serum albumin (g/l)	0.13	0.02–0.24	**.03**			
hs-CRP (mg/l)	−0.69	−1.73–0.35	.2			
nPCR (g/kg/day)	2.56	0.20–4.92	**.04**	2.35	0.1/4.6	**.04**
Serum phosphate (mmol/l)	1.69	0.67–2.72	**.002**			
Serum bicarbonate (mmol/l)	−0.34	−0.57 to −0.10	**.006**			

Significant values are in bold.

Table 4: Univariate and multivariate analysis of variables associated with the TUG test ($n = 114$).

	Unadjusted linear regression analysis			Multivariate linear regression analysis		
Parameters	Coefficient	95% CI	*P*-value	Coefficient	95% CI	*P*-value
Age (years)	0.16	0.08–0.25	**<.001**	0.11	0.02–0.2	**.02**
Gender	−1.16	−4.13–1.80	.44			
CCI	0.87	0.35–1.39	**.001**			
Diabetes mellitus	0.02	−2.96–2.99	.99			
spKt/V	1.27	−2.97–5.51	.56			
Dialysis vintage (years)	0.06	−0.08–0.21	0.40			
BMI (kg/m^2)	0.06	−0.21–0.34	0.65			
Pre-dialysis systolic BP (mmHg)	−0.05	−0.12–0.01	0.10			
Pre-dialysis diastolic BP (mmHg)	−0.08	−0.15 to−0.01	**0.03**			
MVF handgrip (Nm)	−0.29	−0.43 to−0.15	**<0.001**	−0.25	−0.4 to −0.11	**<.001**
Sarcopenia	7.15	4.3–10	**<.001**			
FTI (kg/m^2)	0.12	−0.10–0.35	0.27			
LTI (kg/m^2)	−0.3	−0.75–0.15	0.19			
Creatinine index (mg/kg/day)	−1.12	−1.66 to −0.58	**<0.001**			
Serum albumin (g/l)	−0.48	−0.78 to −0.18	**0.002**			
hs-CRP (mg/l)	0.39	−2.40–3.19	0.78			
nPCR (g/kg/day)	−8.29	−14.51 to −2.08	**0.01**	−8.33	−14.71 to −1.95	**.01**
Serum phosphate (mmol/l)	−3.69	−6.45 to −0.93	**.01**			
Serum bicarbonate (mmol/l)	0.18	−0.47–0.83	.59			

Significant values are in bold.

multivariate analysis, only the balance test remained protective against mortality [HR 0.64 (95% CI 0.46–0.88); $P < .007$] (Table 2).

Determinants of TUG time and SPPB total score

Clinical and biological characteristics according to SPPB total score and TUG time are summarized in Tables 3 and 4. Older age, poor muscle parameters (weakness assessed by low handgrip strength and muscle atrophy assessed by the creatinine index) and albumin reduction were associated with a lower SPPB total score and a longer TUG time. In AIC-based multivariate modelling, age, handgrip strength and nPCR were highly associated with SPPB total score ($P < .05$) (Table 3) and TUG time (Table 4).

The determinants of balance, included in the overall score of the SPPB, were older age, decreased muscle strength, muscle atrophy and malnutrition, as estimated by albumin, nPCR, plasma bicarbonate level and plasma phosphate level in the univariate analysis. Older age, decreased muscle strength and reduced protein intake (nPCR) were still associated with reduced balance in the multivariate analysis (Supplementary Data, Table S2).

DISCUSSION

Our results show that frailty was present in 36–40% of HD patients, depending on the test used (TUG or SPPB). In addition, total SPPB score was associated with a significant independent risk of mortality. Furthermore, muscle weakness and malnutrition were important determinants of frailty in these patients.

In the HD population, frailty prevalence was greater than in general elderly population. Indeed, a large meta-analysis showed that frailty, mainly assessed by the Fried frailty phenotype, could be detected in 30–50% of patients. Here, the prevalence of frailty was found to be 34.3% (CI 24.5–44.1) to 46.0% (CI 34.2–58.3) [22]. This great prevalence of frailty could be due to the dialysis procedure or the uraemic milieu, since SPPB gradually decreases from stage 1–2 to stage 3 (−0.51 points), stage 4 (−0.61 points) and stage 5 prior to dialysis (−1.75 points) [23]. Bioincompatibility of the dialysis process could conspire with uraemic toxins and contribute to frailty by negatively impacting muscle mass. This occurs through mechanisms such as the stimulation of inflammatory pathways and disruption of muscle metabolism, thereby exacerbating sarcopenia. The accumulation of uraemic toxins promotes a chronic inflammatory response and oxidative stress, which constitute key factors in frailty. These deleterious processes are often associated with reduced resilience and increased susceptibility to the development of frailty. Clearly, frailty is associated with a poor outcome, including a decrease in bone mass [24], hospitalization [25] and all-cause mortality [26–30]. However, numerous indexes of frailty have been used in the HD population without any consensus and the prevalence of frailty varies widely across the indexes used. For example, in a recent study involving 315 HD patients, frailty was detected in only 14.6% of the patients using the Study of Osteoporosis Fracture Index (SOF) compared with 33.7% when using the Frail Screening Index. Interestingly, the SPPB, which detected 29.2% of patients, had the best degree of agreement with the Fried frailty phenotype and showed the highest HR, with poor outcome defined as all-cause hospitalizations, fractures and/or all-cause mortality [1.79 (95% CI 1.11–2.88)] [8]. In addition, the reliability of the SPPB and TUG tests, used in the general population and in CKD [23], has been considered suitable in HD patients [9].

Patients included in our study were selected during a relatively stable phase of their medical journey and were able to perform functional frailty assessments, suggesting a better functional health status compared with the overall HD population. Thus, even in patients with apparent better health, frail patients could be identified to predict poor outcome. In the Cox model, after adjustment for all traditional factors of mortality, including CRP, albumin, age, dialysis time, muscle strength (handgrip), muscle mass (creatinine index), presence of sarcopenia and nutritional status (nPCR), a low SPPB score (indicative of frailty) remained an independent risk factor in this seemingly healthier population of HD patients. Therefore, it becomes imperative to include simple tools such as the SPPB and TUG in the clinical evaluation of dialysis patients.

Our results confirm and extend previous results showing that SPPB and TUG constitute functional markers that can be used in chronic HD patients [8, 31]. Our results highlight differences between the tests, indicating that a lower SPPB total score was a more effective predictor of mortality compared with a longer TUG time in HD patients. This may be due to the fact that SPPB measures multiple aspects of physical performance, including balance, gait speed and muscle strength, while TUG only measures the time it takes to stand up from a chair, walk a short distance and sit back down [9, 31]. Therefore, the SPPB may provide a more comprehensive evaluation of physical performance and functional capacity in HD patients, which could explain its stronger association with mortality in this study [8]. Among different SPPB components, the balance test was the most predictive of all-cause mortality. In CKD patients, postural instability, related to muscle dysfunction, is correlated with glomerular filtration rate [32], leading to balance and gait disturbances in HD patients [33]. The crucial role of balance in the functional capacity of HD patients is further supported by the key role of centre of pressure displacement in subjective and objective physical limitations [34]. This decrease in agility may be related to various factors such as aging, decreased proprioception and sarcopenia, which are very common in HD patients.

Both frailty and sarcopenia are related to muscle dysfunction and contribute to the loss of functional capacity and ultimately premature death. Sarcopenia is prevalent in HD patients (≈25% of patients are affected), depending on the diagnostic criteria used [35]. Our study's findings align with this prevalence, indicating a rate of 28%. Furthermore, the literature strongly supports the connection between sarcopenia and mortality, which is consistent with the results of our study [36]. Weakness in association with muscle atrophy contributes to the loss of functional capacity, frailty and ultimately premature death [11, 16]. Initial studies suggest that frailty and sarcopenia are physiologically interrelated, but sarcopenia should not be considered as a surrogate of frailty in HD patients. Indeed, frailty is more related to age-related decline in physiological reserve, while sarcopenia in HD patients is mainly dependent on physical inactivity, uraemic milieu, chronic inflammation related to PEW and muscle contractile quality [15, 35]. In addition, the molecular pathways of sarcopenia in ageing and in HD are different [37].

In our study, we emphasized the importance of muscle function, as we examined three physical performances using the SPPB test: gait speed, muscle strength in the lower limbs and standing balance. Muscle strength emerges as a better predictor of mortality than muscle mass, surpassing the significance of sarcopenia [14, 15]. This study further supports the notion that muscle dysfunction, including weakness and gait speed, is more closely associated with mortality compared with muscle mass alone [14, 28]. In addition to muscle strength, age and protein malnutrition assessed by nPCR appear as the primary determinants of SPPB and TUG (Tables 3 and 4). Our study reinforces the importance of nutrition in HD patients, as it demonstrates the close relationship and the shared determinants between SPPB and TUG, while confirming the impact of nutrition on these patients [29].

Since the main determinant of frailty is muscle strength, muscle rehabilitation could appear as a therapeutic option. According to a meta-analysis including 27 studies and 1156 participants, exercise increases both TUG, SPPB and strength [38]. Similarly, after 12 weeks, an intradialytic aerobic exercise program ameliorated frailty, as reflected by the Fried frailty score ($P < .001$), gait speed ($P < .001$), physical activity ($P < .001$), exhaustion ($P = .002$) and SPPB score ($P = .002$) [39]. Recently, we showed that pre-dialytic exercise training improved the SPBB score and one-leg balance [40].

Our study recognizes some limitations. The sample size is not very large. However, it is relatively appropriate for a study of this nature, which often faces difficulties in recruiting patients in this specific population. It is possible that other factors may contribute to mortality in HD patients, but usual factors such as BP, the presence of diabetes, comorbidities and dialysis adequacy were taken into account. The classical indicator of

dialysis efficiency, Kt/V, might not fully capture the quality of purification, especially regarding nutrition and frailty. Kt/V is influenced by urea distribution volume, which is affected by muscle mass. In order to provide a more in-depth and relevant assessment of dialysis adequacy, the measurement of pre- and post-dialysis β_2-microglobulin was analysed as a reflection of middle molecules. Our study does not take into account the predialytic haemodynamic instability. However, the incorporation of SPPB and TUG parameters in our analysis extends beyond the constraints of the dialysis session.

Finally, this is a cross-sectional study that does not consider the potential change in frailty or other risk factors such as hs-CRP, albumin and nutritional parameters over time. In a large cohort of 762 participants, the Fried frailty score did not remain static from year to year. However, there was almost as much improvement as decline [28].

CONCLUSION

In conclusion, this study highlights the high prevalence of frailty among HD patients and its significant association with increased mortality risk. The utilization of functional performance measures like SPPB and TUG proves valuable in assessing frailty, with SPPB offering comprehensive insights by incorporating balance assessment. Notably, diminished muscle strength and inadequate protein intake emerged as key determinants of balance in HD patients. These findings suggest that identifying and managing frailty in HD patients is crucial to improve their outcomes and quality of life.

SUPPLEMENTARY DATA

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

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DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

CONFLICT OF INTEREST STATEMENT

All authors declare they have no conflicts of interest.

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