


ARTICLE



Nutrition in acute and chronic diseases

Quadriceps muscle thickness assessed by ultrasound is independently associated with mortality in hemodialysis patients

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BACKGROUND/OBJECTIVES: Estimation of muscle mass is an integral part of nutritional assessment in End-Stage Kidney Disease (ESKD) patients on chronic hemodialysis (HD). In this respect, muscle ultrasound (US) is a valid and reliable tool but has not been previously related to outcomes in this population. Aims of this study were to assess the relationship between quadriceps muscle thickness as assessed by US and outcomes in ESKD patients on HD; we also compared US with anthropometry and malnutrition inflammation score (MIS).

SUBJECTS/METHODS: In this prospective study, 181 prevalent patients on HD were included. Thickness of the quadriceps rectus femoris and vastus intermedius (VIT) were assessed separately using ultrasonography, and were indexed for height squared. Mid-arm muscle circumference (MAMC) and area (MAMA) were assessed by anthropometry. MIS was evaluated. In the absence of predetermined cut-offs, values below the median of the distribution of VIT index were considered low. Instead, cut-off for anthropometric values such as MAMC and MAMA were set at $\geq 90\%$ of agreement with the 50th percentile of the sex- and age-specific normal distribution. Cox-regression analysis was used to assess the association of US, MIS, and anthropometric parameters with mortality.

RESULTS: Patients were followed for a median of 35 months. During this period 36% of patients died. Multivariable Cox-regression analysis (adjusted for demographic, biochemical and clinical variables), demonstrated that higher VIT distal index values were independently associated with lower mortality risk (HR: 0.76 (0.59–0.99); $P = 0.040$), whilst higher MIS values were independently associated with higher (HR 1.22 (1.10–1.35); $P < 0.001$) mortality risk. When assessing muscle parameters as categorical variables, both low VIT distal index (HR: 1.71 (1.01–2.89); 0.045) and MAMC (HR: 1.74 (1.02–2.96); 0.042) were independently associated with increased risk of death.

CONCLUSION: Indexed distal VIT was independently associated with mortality both as continuous and as a categorical variable. Muscle US is a simple practical tool that adds prognostic information to the bedside nutritional assessment in ESKD patients on maintenance HD.

European Journal of Clinical Nutrition (2022) 76:1719–1726; <https://doi.org/10.1038/s41430-022-01166-7>

INTRODUCTION

End-stage kidney disease (ESKD) is a catabolic condition also characterized by reduced protein synthesis [1]. This imbalance between catabolism and anabolism results in muscle loss. In fact muscle loss, despite being also dependent on physiological ageing, occurs earlier and more rapidly in patients on hemodialysis (HD) in comparison to age-matched controls [2, 3]. Reasons for the increased protein catabolism include the metabolic consequences of the loss of kidney function, the lifesaving kidney replacement therapy, and the presence of other chronic comorbidities [1].

Skeletal muscle is vital to mobility, posture, strength and balance, allowing for routine physical activities and exercise [4]. In addition, it is also a pivotal metabolic and homeostatic organ [5]. Most importantly, it plays a key role in protein metabolism as a source of amino acids when protein intake is insufficient, thus preserving the protein content of other essential organs [5, 6]. However, when muscles undergo chronic catabolism to supply amino acids for other metabolic purposes, without parallel activation of a compensatory increased protein synthesis, a reduction in muscle mass is observed. This very fact has potentially serious clinical consequences such as

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Received: 20 December 2021 Revised: 12 May 2022 Accepted: 16 May 2022

Published online: 31 May 2022

muscle weakness, impaired physical function, and increased morbidity and mortality [7].

Consequently, an important part of the routine nutritional evaluation of patients on chronic HD is the assessment of body composition, which typically refers to the quantification of adipose tissue and muscle mass [8]. Since the identification of reduced muscle mass is critical, a precise and accurate method that is also economically sustainable should be the preferred approach to assess muscle wasting, aiming for an early diagnosis and monitoring in patients at risk of muscle loss. Currently, the most frequently used tools to estimate muscle status at the bedside are anthropometry and bioimpedance methods. However, both methods have intrinsic limitations that hamper the accurate assessment of muscle status. Specifically, both techniques can be influenced by fluid overload [9, 10], which occurs frequently in patients on HD. In this regard, the use of ultrasound (US) for the measurement of muscle dimensions has received considerable interest in recent years. In fact, this diagnostic technique can be performed easily at the bedside even in non-collaborative patients, it is safe, economically sustainable, and does not require specialized staff or X-ray exposure [11–13]. The reliability of US in measuring quadriceps muscle thickness has recently been documented both in critically ill patients with AKI [12], in whom it has also been validated against CT [14], and in ESKD patients on HD [11]. Importantly, muscle US is not affected by alterations of fluid status [12, 13], which are very common in this clinical setting and represent one of the principal problems in applying currently available bedside techniques [15]. In the absence of tools to assess muscle status, the Malnutrition Inflammation Score (MIS) and the Subjective Global Assessment (SGA), have been frequently used to identify malnourished patients in hemodialysis [16]. Although they do not allow for quantitation of muscle mass, MIS and SGA assessments include a physical evaluation section to assess muscle status; in addition, both have an important prognostic value since patients with MIS scores above 8 [17], and patients considered malnourished by SGA [18], have increased risk of mortality. Conversely, the relationship between muscle status as assessed by US and mortality has not yet been studied in the renal setting.

In the present study, we aimed to assess the association of quadriceps muscle thickness by US with mortality in patients on maintenance HD; in addition, we compared the associations with mortality of US, with anthropometry, MIS and SGA.

MATERIALS/SUBJECTS AND METHODS

Study design and patients

This is a secondary analysis of an ongoing observational prospective study of 181 prevalent patients on maintenance HD from 6 dialysis centers in northern and central Italy (3 located in Parma, 1 in Reggio Emilia and 2 in Livorno) [13]. The total patient capacity in the 6 centers during the period of study was 350 patients. The study was approved by the local Institutional Review Board (AVEN ref. no 45737, December 12th, 2015). The procedures were in agreement with the Declaration of Helsinki, and written informed consent was obtained from all participants. Patients were evaluated between January 1st, 2016 and March 31, 2018, and followed for mortality until May 31st, 2020. The main objective of this cohort study was to assess the relationship between muscle mass as assessed by US and other nutritional parameters [13]. Only adult patients (≥ 18 years of age) with a dialysis vintage of at least 6 months were enrolled. Patients with malignancy or with conditions associated with mandatory immobilization (i.e. paralysis, amputation of the lower limbs) were excluded.

Demographic and clinical variables

Age, sex, HD vintage, comorbid conditions (i.e. presence of diabetes, COPD, cardiovascular diseases and heart failure) were collected at baseline from medical records. Blood samples were collected pre-dialysis as per institutional routine, preferably on a

midweek dialysis day, for assessment of serum creatinine, blood urea nitrogen (BUN), albumin, and C-reactive protein (CRP).

Ultrasound technique

Quadriceps rectus femoris and vastus intermedius thickness (QRFT and QVIT) were measured by experienced assessors using B-mode ultrasonography with a wall-tracking ultrasound system (Philips hd7xe, Logiq, and General electric) and 7.5 MHz linear array transducers. The technique used has already been described in detail previously [12, 13, 19]. Briefly, measurements were performed at two landmarks for each leg with the patient lying in a supine position with both knees extended but relaxed and toes pointing to the ceiling, during the HD session. Quadriceps rectus femoris and vastus intermedius thickness (RFT; VIT) were measured at the mid-point (RFT Prox; VIT Prox) and at the border between the lower third and upper two-thirds (RFT Dist; VIT Dist) of the distance between the anterior superior iliac spine (ASIS) and the upper pole of the patella [12, 20] (Supplementary material 1). The transducer was placed perpendicular to the long axis of the thigh with a large amount of gel and with minimal pressure to avoid compression of the muscle. The assessor was positioned on the side of the patient while performing the measurements, and was allowed to tilt the probe or move it laterally to obtain the best possible image, in which RF and VI would be aligned and centered. The vertical thickness of the muscle was measured at the widest point, on the inner edge of the muscle fascia. Measurements were performed directly on line while obtaining the images. Three experienced assessors (1 for all centers in Parma and Reggio Emilia, 1 for each center from Livorno), all of whom had received previously formal training on the described method, as described in our reliability study [12], and had performed at least 100 supervised measurements, performed all measurements. Two measurements on both legs for each site were averaged and were used for the analysis (a total of 4 values for each subject). The coefficient of variation (CV) for the 2 measurements performed in each site ranged from 3.2% for the RFT Prox in the left leg to 4.9% for the VIT Dist in the right leg; while the CV for each site between legs ranged from 6.6% for the RFT Prox to 9.4% for the VIT Prox. For further analyses, measurements were normalized by height squared.

Anthropometrics

Anthropometric measurements included body weight, height, mid-arm circumference (MAC) and triceps skinfold (TSKF) thickness, and were assessed after the dialysis session. Body weight (kg) was measured by electronic bed scales and height (m) using a stadiometer. Body mass index (BMI) was calculated as body weight (kg) divided by squared height (m^2). TSKF (mm), is the assessment of the thickness of the skin, including the subcutaneous fat, it was measured using the Lange Skinfold Caliper (Cambridge Scientific Industries Inc., Cambridge, MD, USA) by pinching the skin over the triceps muscle of the arm. MAC, which measures the circumference of the arm at the mid-point between the olecranon process and the acromium, was assessed using a non-stretchable measure tape. Both anthropometric parameters (i.e. TSKF and MAC) were used to calculate the mid-arm muscle circumference (MAMC) and mid-arm muscle area (MAMA) by applying the following equations:

$$\text{MAMC (cm)} = \text{MAC (cm)} - (\pi \times \text{TSKF}_{(\text{cm})})$$

$$\text{MAMA (cm}^2\text{)} = \frac{(\text{MAC (cm)} - [\text{TSKF}_{(\text{cm})} * \pi])^2}{4\pi}$$

and were analyzed based on the percentage of agreement with the 50th percentile of the sex- and age-specific normal distribution available at Frisancho [21].

Table 1. Demographic and clinical characteristics of the entire cohort.

	Overall (n = 181)	Male (n = 123)	Female (n = 58)	Deceased (n = 66)	Alive (n = 115)
Age (years)	65 (16)	66 (17)	64 (16)	73.7 (12.6)	60.8 (16.7)
Male Sex (%)	123/181 (68)	–	–	49/66 (74)	74/115 (64)
Time in study (median; IQR) (months)	35 (22; 41)	34 (20; 41)	36 (26; 41)	19 (8.3; 26.8)	37 (35; 45) [§]
HD vintage (median; IQR) (months)	55 (17; 96)	57 (17; 97)	50 (17; 96)	60 (29; 109)	50 (16; 95)
Body weight (kg)	68.6 (12.8)	71.2 (12.0)	63 (13) ^{***}	68.4 (12.3)	68.7 (13.1)
Height (cm)	166 (8.7)	170 (6.6)	157 (6.3) ^{***}	1.67 (0.09)	1.66 (0.08)
BMI (kg/m ²)	24.8 (4.5)	24.6 (4.2)	25.3 (5.1)	24.5 (4.1)	25.0 (4.7)
MIS ^a	6.7 (3.7)	6.7 (4.0)	6.6 (3.1)	8.6 (4.3)	5.5 (2.7) [§]
7-point SGA (% malnourished) ^a	20/116 (17)	11/75 (15)	9/41 (22)	12/43 (28)	8/74 (11) [§]
Biochemical data					
sCr (mg/dl)	8.7 (3.1)	9.0 (3.3)	8.2 (2.5)	7.9 (2.8)	9.3 (3.2) [§]
BUN (mg/dl)	70.1 (18.7)	67.9 (16.5)	74.8 (22.1)*	66.3 (17.0)	72.4 (19.4) [§]
Albumin (g/dl)	3.7 (0.4)	3.7 (0.4)	3.6 (0.3)	3.6 (0.4)	3.8 (0.4) [£]
CRP (mg/l)	0.87 (0.26; 2.75)	0.95 (0.95; 3)	0.71 (0.22; 2.36)	1.36 (0.51; 3.35)	0.79 (0.19; 2.34) [§]
Comorbidities					
Diabetes (%)	51/181 (28)	36/123 (29)	15/58 (26)	27/66 (41)	24/115 (21) [£]
COPD (%)	15/181 (8)	14/123 (11)	1/58 (2)*	11/66 (17)	4/115 (3.5) [§]
Cardiovascular diseases (%)	77/181 (43)	57/123 (46)	20/58 (34)	41/66 (62)	36/115 (31) [£]
Heart failure (%)	21/181 (12)	16/123 (13)	5/58 (9)	14/66 (21)	7/115 (6) [§]
Anthropometry and muscle US					
Triceps skinfold thickness (mm)	13.1 (6.0)	11.7 (5.3)	16.1 (6.2)**	11.6 (6.5)	14.0 (5.5) [§]
MAC (cm)	28.5 (4.1)	28.1 (3.8)	29.2 (4.8)	27.7 (4.1)	28.9 (4.1) [§]
MAMC (cm)	24.4 (3.2)	24.5 (3.1)	24.2 (3.4)	24.0 (2.9)	24.6 (3.4)
MAMA (cm ²)	48.2 (12.8)	48.6 (12.2)	47.4 (14.1)	46.6 (11.3)	49.1 (13.6)
RFT Prox (mm)	16.1 (4.4)	16.8 (4.5)	14.4 (3.7) ^{***}	14.6 (3.7)	16.9 (4.6) [£]
VIT Prox (mm)	13.1 (4.8)	13.9 (5.3)	11.5 (3.0)**	11.6 (3.4)	14.1 (5.2) [£]
RFT Dist (mm)	10.9 (3.6)	11.4 (3.8)	9.8 (2.9)**	9.7 (3.1)	11.6 (3.7) [£]
VIT Dist (mm)	10.1 (3.4)	10.6 (3.7)	8.8 (2.4) ^{***}	8.9 (2.6)	10.7 (3.7) [£]
RFT Prox index (mm/height ²)	5.8 (1.6)	5.8 (1.6)	5.7 (1.4)	5.3 (1.5)	6.1 (1.5) [£]
VIT Prox index (mm/height ²)	4.8 (1.7)	4.8 (1.8)	4.7 (1.3)	4.2 (1.3)	5.1 (1.8) [£]
RFT Dist index (mm/height ²)	3.9 (1.3)	4.0 (1.3)	3.9 (1.1)	3.5 (1.2)	4.2 (1.3) [£]
VIT Dist index (mm/height ²)	3.6 (1.2)	3.7 (1.3)	3.5 (1.0)	3.2 (1.1)	3.9 (1.2) [§]
Deceased (%)	66/181 (36)	49/123 (40)	17/58 (29)		

*** $P < 0.0001$; ** $P < 0.01$; * $P < 0.05$, female versus male patients; [§] $P < 0.05$; [£] $P < 0.01$; [£] $P < 0.001$, alive versus deceased patients. Data are expressed as mean (SD), median (interquartile range) and frequency (%).

BMI body mass index, BUN blood urea nitrogen, COPD chronic obstructive pulmonary disease, CRP C-reactive protein, HD hemodialysis, MAC mid-arm circumference, MAMA mid-arm muscle area, MAMC mid-arm muscle circumference, MIS malnutrition inflammation score, RFT Rectus femoris thickness, SGA subjective global assessment, VIT vastus intermedius thickness.

^aAvailable for 116 patients.

Subjective global assessment (SGA)

Subjective Global assessment is a validated and well-established composite tool to assess nutritional status widely used internationally in many disciplines beyond nephrology [22]. It is composed of nutritional history (changes in body weight and dietary intake, presence of gastrointestinal symptoms), functional capacity, disease-related comorbidities and physical examination (loss of subcutaneous fat, muscle wasting, and clinical edema). The 7-point SGA was used, as recommended by the new updated KDOQI guideline [23], and patients were classified as well-nourished (score 7–6), mild to moderate malnutrition (score 5–3) and severe malnutrition (score 2–1) [11]. For analysis purposes, patients with SGA score 5–1 were grouped as malnourished. Subjective global assessment was available in 116 patients.

Malnutrition inflammation score (MIS)

Malnutrition inflammation score is a comprehensive evaluation that combines the subjective parameters of SGA, plus objective parameters, such as BMI, serum albumin, and serum transferrin, with a total of 10 components [24]. Each component has four levels of severity, from 0 (normal) to 3 (severely abnormal). The sum of all 10 MIS components can range from 0 (normal) to 30 (severely malnourished). The higher the score value, the more severe is the degree of malnutrition and inflammation. A cut-off of 8 was used to identify malnourished patients [17]. Malnutrition inflammation score was available in 116 patients.

Statistical analysis

Results are expressed as mean and standard deviation for continuous variables with normal distribution, or median and range for non-

Table 2. Univariate Cox-regression analysis for the association of demographic, clinical, biochemical, and nutritional parameters with all-cause mortality.

Variable	HR (95% confidence interval); P
Demographic	
Age	1.04 (1.02–1.06); <0.001
Male sex	1.50 (0.86–2.60); 0.151
HD vintage	1.00 (1.00–1.01); 0.082
Clinical	
Cardiovascular disease	2.81 (1.70–4.62); <0.001
Heart failure	2.84 (1.56–5.16); 0.001
COPD	3.05 (1.59–5.85); 0.001
Diabetes	2.14 (1.31–3.51); 0.003
Biochemical	
Serum creatinine	0.87 (0.81–0.95); 0.001
Blood urea nitrogen	0.98 (0.97–0.99); 0.038
Serum albumin	0.35 (0.20–0.59); <0.001
C-reactive protein	1.02 (1.01–1.03); <0.001
Nutritional	
Body mass index	0.97 (0.92–1.03); 0.363
RFT Prox	0.91 (0.86–0.96); 0.001
VIT Prox	0.90 (0.84–0.96); 0.001
RFT Dist	0.87 (0.81–0.94); <0.001
VIT Dist	0.85 (0.78–0.93); <0.001
RFT Prox index	0.75 (0.64–0.88); 0.001
VIT Prox index	0.72 (0.60–0.86); <0.001
RFT Dist Index	0.68 (0.55–0.84); <0.001
VIT Dist Index	0.64 (0.49–0.82); <0.001
MAMC	0.95 (0.88–1.02); 0.142
MAMC percent of agreement	0.99 (0.98–1.005); 0.199
MAMA	0.98 (0.96–1.00); 0.109
MAMA percent of agreement	0.99 (0.99–1.002); 0.192
MIS ^a	1.25 (1.16–1.35); <0.001
MIS > 8 ^a	3.81 (2.08–6.98); <0.001
SGA	2.48 (1.27–4.84); 0.008

COPD chronic obstructive pulmonary disease, HD hemodialysis, MAMA mid-arm muscle area, MAMC mid-arm muscle circumference, MIS malnutrition inflammation score, RFT rectus femoris thickness, SGA subjective global assessment, TSKF triceps skinfold, VIT vastus intermedius thickness.

^aAvailable in 116 patients.

parametric data, and as frequencies for categorical variables. Group differences were analyzed using Student *t* test and Mann-Whitney's *U* test for continuous data as appropriate, and χ^2 or the Fisher's exact for categorical variables. The correlation between quadriceps muscle thickness index and demographic or clinical variables was assessed by univariate linear regression. Cox proportional hazards models were used to estimate the association between all-cause mortality and quadriceps muscle thickness index, MIS, MAMC, and MAMA, both as continuous and categorical variables. Multivariable analysis was performed by adjusting the model for those variables that were simultaneously associated with mortality ($P < 0.10$) and with VIT distal index at univariate analysis (age, serum creatinine, serum albumin, diabetes and cardiovascular disease). In the absence of published reference values, we also tested the association of US muscle parameters with mortality using the median value of the VIT distal

index distribution. In the case of MAMC and MAMA, based on published reference values [8], we divided our sample in 2 groups based on values $<$ or $\geq 90\%$ of agreement with the corresponding sex and age specific 50th percentiles and Kaplan–Meier survival curves were fitted. The Akaike information criterion (AIC) was used to compare the performance of US models (i.e., the binary vs continuous) in relation to the risk of death. All analyses were performed using IBM Statistical Package for Social Sciences version 26.0 (IBM SPSS Statistics Inc. Chicago, IL, USA).

RESULTS

Clinical and demographic characteristics of enrolled patients

Patient baseline characteristics are summarized in Table 1. We enrolled 181 patients, (123 males [68%], mean age 65 ± 16 years). Males and females differed by dry body weight and height (but not BMI), blood urea nitrogen (BUN), prevalence of chronic obstructive pulmonary disease, and all absolute values of quadriceps muscle thickness. However, when muscle thickness was normalized by height squared (QRFT and QVIT index), no difference was found between males and females.

Follow-up and outcome of HD patients

Overall, patients were followed for a median of 35 months (interquartile range [IQR], 22–41 months). During this period, 36% (66/181) of the patients died. The main cause of death was cardiovascular conditions in 38.8% of patients, followed by sepsis (22.4%), cachexia/malnutrition (11.9%) and malignancy (10.4%), in 16.4% the cause of death was not ascertained. Nonsurvivors were older, were more inflamed, presenting lower serum albumin, and higher serum CRP than survivors. In addition, the former had higher prevalence of all assessed comorbidities (i.e. diabetes, COPD, cardiovascular diseases, and heart failure) and lower muscle thickness as assessed by US (Table 1).

Associations of quadriceps muscle thickness, MAMC, MAMA, and MIS with all-cause mortality

At univariate Cox-regression analysis, higher muscle thickness was associated with less chance of mortality for all muscle US parameters. Indexed muscle US parameters, and particularly RFT Distal Index (HR: 0.68 (0.55–0.84); $P < 0.001$) and VIT Distal index (HR: 0.64 [0.49–0.82]; $P < 0.001$) showed the strongest associations (Table 2). Regarding anthropometric variables, absolute values of MAMC (HR: 0.95 (0.88–1.02); $P = 0.142$) and MAMA (HR: 0.98 (0.96–1.00); $P = 0.109$), and the percent of agreement of these measures in relation to the corresponding 50th percentile of the sex- and age-specific normal distribution (MAMC HR: 0.99 (0.98–1.005); $P = 0.199$; MAMA HR: 0.99 (0.99–1.002); $P = 0.192$), were not associated with mortality. Conversely, higher age, the presence of chronic comorbidities, higher MIS, worse SGA, low serum albumin, low blood urea nitrogen, low serum creatinine, and higher C-reactive protein were significantly associated with increased mortality risk (Table 2).

We also investigated the correlation between demographic, clinical, and biochemical variables with quadriceps muscle US parameters, using VIT distal index as the parameter of reference (Table 3). We found that high age, low BMI, low serum creatinine, low serum albumin, and the presence of cardiovascular disease were all associated with reduced muscle thickness. As VIT distal index and RFT distal index were the US parameters which had the strongest association with mortality at univariate analysis, we tested both for mortality. At multivariable Cox-regression analysis (Table 4), only VIT distal index was strongly and independently associated with mortality, along with MIS (both as continuous and categorical variables). Notwithstanding that MAMA, as percent of agreement in relation to the 50th percentile of the sex- and age-specific values, had a significant negative association with mortality, the observed decreased hazard of death for each 1%

Table 3. Correlation between demographic and clinical variables with VIT distal index.

Variable	R (Standard error)	P value
Age	-0.018 (±0.005)	0.001
Sex	0.127 (±0.196)	0.518
HD vintage	-0.001 (±0.001)	0.467
BMI	0.103 (±0.019)	<0.001
Serum creatinine	0.084 (±0.029)	0.004
Blood urea nitrogen	0.000 (±0.005)	0.924
Serum albumin	0.858 (±237)	<0.001
C-reactive protein	-0.008 (±0.005)	0.152
Diabetes	0.358 (±0.202)	0.078
Cardiovascular disease	-0.394 (±183)	0.033
COPD	-0.47 (±0.332)	0.888
Peripheral vascular disease	-0.152 (±0.202)	0.454
Heart failure	-0.170 (±0.286)	0.554

BMI body mass index, COPD chronic obstructive pulmonary disease, HD hemodialysis.

Table 4. Multivariable Cox-regression analysis for the association of nutritional parameters with all-cause mortality in end-stage kidney disease patients on hemodialysis ($n = 181$).

Variables	HR (95% confidence interval); P
VIT Distal index	0.76 (0.59–0.99); 0.040
RFT Distal index	0.83 (0.67–1.04); 0.108
MAMC	0.94 (0.86–1.02); 0.126
MAMC percent of agreement	0.99 (0.98–1.001); 0.079
MAMA	0.98 (0.96–1.00); 0.070
MAMA percent of agreement	0.99 (0.99–1.00); 0.041
MIS ^a	1.22 (1.10–1.35); < 0.001
MIS > 8 ^a	2.13 (1.06–4.31); 0.034
SGA	1.65 (0.76–3.60); 0.205

All models were adjusted for age, serum creatinine, serum albumin, diabetes, and cardiovascular disease.

MAMA mid-arm muscle area, MAMC mid-arm muscle circumference, MIS malnutrition inflammation score, RFT rectus femoris thickness, SGA subjective global assessment, VIT vastus intermedius thickness.

^aAvailable for 116 patients.

increase in MAMA could hardly be considered clinically important. SGA, on the other hand, was not independently associated with mortality in the multivariate analysis.

Subsequently, we tested the association between dichotomized muscle parameters (VIT Distal index, RFT Distal index, MAMC, and MAMA) with all-cause mortality. Kaplan–Meier survival curves show that VIT distal index and RFT distal index below the median and MAMC below 90% of agreement with the 50th percentile were associated with reduced survival in ESKD patients on HD (Fig. 1). Similar results were obtained at both univariate and multivariable Cox-regression analyses, except for RFT Distal index (Table 5).

Akaike information criteria was slightly lower (1169.44 versus 1170.01) for the model using VIT distal index as a continuous vs dichotomized variable.

DISCUSSION

In this prospective study we investigated the association of quadriceps muscle thickness as assessed by US, MAMC, and

MAMA as surrogate markers of muscle mass, and MIS with all-cause mortality among patients with ESKD on chronic HD. We found that VIT distal index below the median, lower MAMC, and higher MIS were independently associated with mortality. When we modeled the same parameters as continuous rather than dichotomized variables, we found that VIT distal index, MAMA as percentage of agreement with the sex- and age-specific 50th percentile of the normal distribution, and MIS were independently associated with long-term outcomes. The model with dichotomized VIT distal index had similar predictive performance compared to the model with continuous VIT distal index.

To our knowledge, this is the first time that muscle US was used to assess the risk of mortality in ESKD patients on chronic HD. The association of muscle dimensions with outcomes has been explored previously in this population, showing that reduced muscle mass as assessed by body composition or surrogate methods increase the risk of worse outcomes [25–30]. In fact, muscle wasting is very common in patients with ESKD on HD [13, 31, 32], as it is a consequence of metabolic acidosis, chronic inflammation, and anorexia related to the kidney disease per se, as well as of renal replacement therapy and comorbidities associated with increased protein catabolism and reduced protein anabolism, eventually resulting in muscle loss [1]. Despite its recognized importance, the assessment of muscle mass is challenging in renal patients. Current bedside methods (such as anthropometry and bioimpedance spectroscopy [BIS]) have important limitations, both intrinsic to the methods and also caused by fluid balance derangements typical of this clinical setting [33].

Traditionally, MAMC has been widely used as an index of muscle mass in clinical practice, and has been recommended by the International Society of Renal Nutrition and Metabolism (ISRNM) for establishing a diagnosis of protein-energy wasting [8]. However, its diagnostic value in the context of sarcopenia and its predictive role towards hard outcomes in patients with CKD/ESKD are still controversial. In a previous study, our group demonstrated a weak positive correlation between MAMC and quadriceps muscle US [13]. Moreover, when comparing values of abdominal skeletal muscle mass as assessed by CT with those assessed by surrogate methods, MAMC had only a moderate correlation with the reference method [34]. Regarding outcomes of patients with CKD on conservative treatment, MAMC with < 90% of adequacy relative to the p50 value of age- and gender-specific distribution was used to identify patients with low muscle mass; [29] in the study by Pereira et al, low MAMC, combined with handgrip strength (HGS), was associated with survival only in the non-adjusted analysis [35]. In another study in ESKD patients on HD, MAMC as a continuous variable had no association with mortality [34]. Conversely, in an earlier study where MAMC was identified as percentage of agreement and analyzed as a continuous variable, this parameter independently predicted mortality [36]. Unlike MAMC and MAMA, quadriceps muscle US was independently associated with mortality when modeled as either a continuous or a categorical variable. MAMC measurements are inaccurate in the case of fluid overload, as opposed to muscle ultrasound [12, 13]. Moreover, ultrasound machines are easily available in dialysis centers, and measurements can be performed during dialysis session. Furthermore, it has been suggested that the assessment of muscle mass of lower limbs is particularly valuable in predicting clinical outcomes of patients on chronic HD because of its strong association with functional outcomes [37]. Another plausible explanation is that prolonged inactivity in nonsurvivors may have affected lower and upper limb muscles disproportionately, with a greater impact on quadriceps muscle, and thus MAMC and MAMA may overestimate lean muscle mass. In fact, Fukasawa et al showed that lower thigh muscle CSA as assessed by CT was significantly associated with all-cause and cardiovascular mortality in elderly patients on HD [38]. Moreover, Tsukasaki et al suggested that the assessment of muscle mass of lower extremities is

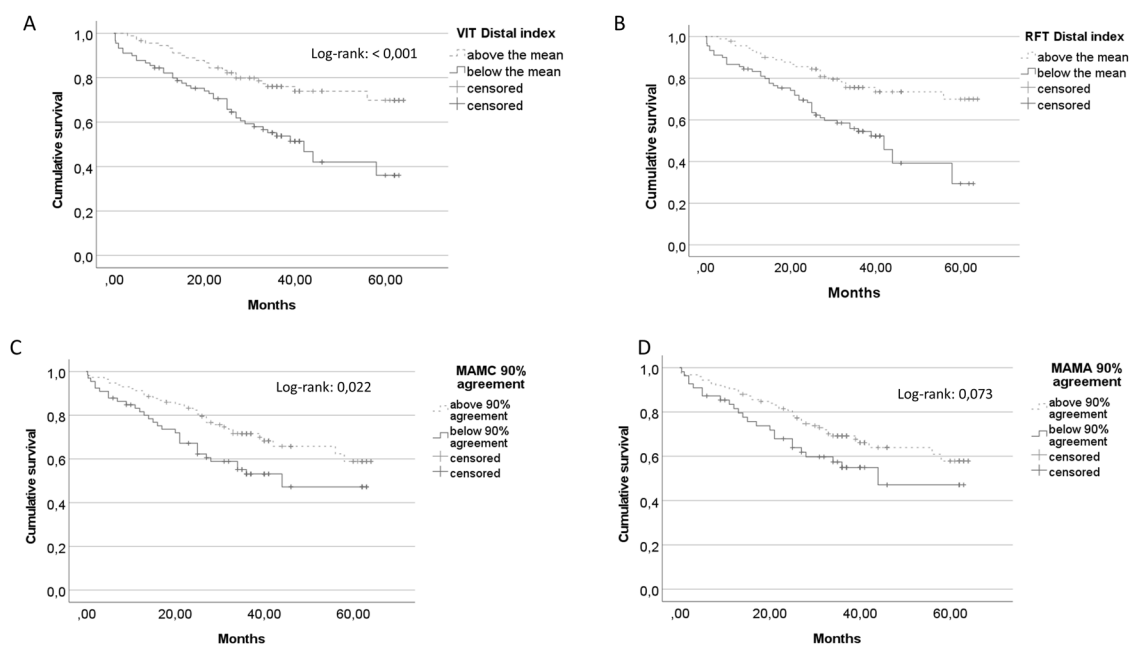


Fig. 1 Kaplan–Meier survival curves of patients with end-stage kidney disease on hemodialysis ($n = 181$) with low muscle status. **A** Low muscle status by VIT distal index below the median **(B)** Low muscle status by RFT distal index below the median **(C)** Low muscle status by MAMC below 90% of agreement with age and gender-specific p50 **(D)** Low muscle status by MAMA below 90% of agreement with age and gender-specific p50.

Table 5. Univariate and multivariable Cox-regression analysis for the association of indexed muscle parameters as categorical variables with all-cause mortality in end-stage kidney disease patients on hemodialysis ($n = 181$).

Variables	HR (95% confidence interval); P
Univariate analysis	
VIT Distal index below the median	2.41 (1.45–4.00); 0.001
RFT Distal index below the median	2.46 (1.47–4.11); <0.001
MAMC < 90% agreement p50	1.75 (0.1.07–2.84); 0.024
MAMA < 90% agreement p50	1.56 (0.95–2.61); 0.077
Multivariable analysis ^a	
VIT Distal index below the median	1.71 (1.01–2.89); 0.045
RFT Distal index below the median	1.57 (0.90–2.74); 0.113
MAMC < 90% agreement p50	1.74 (1.02–2.96); 0.042
MAMA < 90% agreement p50	1.60 (0.94–2.72); 0.083

MAMA mid-arm muscle area, MAMC mid-arm muscle circumference, RFT rectus femoris thickness, VIT vastus intermedius thickness.

^aAdjusted for age, serum creatinine, serum albumin, diabetes and cardiovascular disease.

particularly valuable in predicting clinical outcomes of patients on chronic HD because of its strong association with functional outcomes [37].

The reliability of quadriceps muscle US has been reported in critically ill patients with AKI, with excellent intraclass correlation coefficient (ICC) for inter- and intra-operator comparisons [12]. In the same clinical setting, the methods used in the present study have been validated recently against CT with small, non-statistically significant differential and proportional bias [19]. In addition, available data suggest that US is unaffected by fluid overload and rapid fluid shifts, such as those typical of ESKD patients on HD [12, 13]. Quadriceps muscle US has also been used

in patients with CKD on conservative treatment for the assessment and validation of muscle cross-sectional area (CSA) [39]. More recently, quadriceps CSA cut-offs have been derived using receiver-operation characteristic (ROC) curves to identify patients with PEW in a Malaysian population [40]. Interestingly, quadriceps muscle thickness of RF and VI reported in our study were lower, probably because our sample is of different ethnicity and specially because it included older patients. The present study confirms data reporting an association between low quadriceps muscle mass and mortality in patients on hemodialysis [38], but it is the first time that US has been used to investigate such association in this clinical setting. Recently, we showed that US is a sensitive tool to assess changes in quadriceps muscle thickness over time [41].

Malnutrition inflammation score and SGA are well-established predictors of poor outcomes in patients on HD, they are two simple and inexpensive tools also recommended by the 2020 NKF/KDOQI Nutrition guidelines for routine nutritional assessment [23]. In the present study we also found that MIS had a strong association with mortality, and this association was stronger than anthropometric and US measures of muscle dimensions. That result was not unexpected, since MIS is a composite tool that evaluates nutritional and non-nutritional factors, such as inflammation and disease-related comorbidities [22]. On the other hand, SGA lost its significance at multivariable Cox-regression analysis, probably due to insufficient study power. However, the superiority of MIS in comparison to SGA in predicting mortality has already been demonstrated by other investigators [18, 42]. While SGA is a component of MIS, the reason why MIS has a stronger association with mortality than SGA may reside in the inclusion of inflammation markers (i.e., albumin and C-reactive protein) in the former. Although the clinical importance of SGA and MIS as prognostic tools is well recognized, MIS does not allow for an accurate evaluation of muscle status following physical and nutritional rehabilitation. In fact, an improvement in both composite tools could be related to increased appetite and food intake, decreased gastrointestinal symptoms, increased dry body weight, or even improvement of inflammation, whereas muscle status could remain unchanged. While both scores provide

important information for an initial evaluation of nutritional status, the US technique can be used for an accurate evaluation of muscle status following physical and nutritional rehabilitation. In fact, we recently demonstrated that quadriceps muscle US is a sensitive tool to detect changes over time, as it was applied in critically ill patients with acute kidney injury [41].

It is important to address the limitations of our study, as well as the possible limitations for the use of US for the assessment of muscle mass. Firstly, as we did not enroll a control group of healthy subjects, it was not possible to study cut-off values derived from a normative population, as is recommended by the European Working Group on Sarcopenia in Older People (EWGSOP) [43]. While we found a strong and significant association of distal VIT index modeled as a continuous variable with mortality, we also tested this association by modeling distal VIT index as a dichotomized variable based on the median of its distribution values. Although this cut-off was chosen arbitrarily, this is a common approach when an accepted cut-off for a given potential predictor in a time-to-event analysis is not available [44–48]. Therefore, further investigations are warranted to identify threshold values based on normative populations to evaluate and define low quadriceps muscle thickness in larger populations of ESKD patients on HD. Secondly, given the small sample size of female patients, we were not able to perform analysis stratified by sex. However, the correction of quadriceps muscle thickness by height squared removed all differences between male and female subjects. Thirdly, our study did not include measures of muscle strength (e.g., handgrip strength), which represents an important functional component of sarcopenia. Finally, the assessment of muscle thickness by US may be operator dependent, the pressure applied on the probe may deform the muscle, limiting its use by untrained operators. To allow for an accurate image acquisition and measurement, it's important to use excess contact gel between the probe and the skin, in order to put as little pressure as possible. In addition, we already showed that non-experienced operators that have received formal training and followed a standardized protocol have high intraclass correlation coefficients [12]. Nonetheless, it's recommended that the same operator perform repeated measures over time to monitor individual patients to avoid measurement bias. Despite the above limitations, to our knowledge the association of quadriceps muscle thickness with mortality has not been investigated previously in ESKD patients. It is also the first time that a bedside imaging method, that has already been shown to be precise and accurate, is used to study this association. Furthermore, image acquisition and measurement is fast, taking less than 15 min to perform, US machines are cheap and widely available in dialysis clinics because they are used to control arteriovenous fistulas, with no need to invest in particular instruments. Taken together, the use of US to assess quadriceps muscle is not only clinically feasible, but also economically viable. Finally, our study may add useful information in the field of research on accurate diagnostic techniques that can be used at the bedside to assess muscle mass in severely catabolic patients, as those with ESKD.

In conclusion, we found a strong direct association of VIT distal index with mortality in patients with ESKD on maintenance HD. Based on the available evidence, we suggest that quadriceps muscle US could have a role in the assessment and monitoring of patients over time, as decreasing muscle thickness index may predict poor outcomes in other clinical settings, although data from patients on chronic hemodialysis are still lacking. Moreover, muscle US could add relevant information to multidimensional predictive models in HD patients, and could be used to detect warning signals for impending PEW or sarcopenia in this population.

DATA AVAILABILITY

The data analyzed during this study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

AS was responsible for designing the protocol, data collection, and analysis, as well as writing the manuscript. JPK, mentorship and contribution to writing the manuscript. TDM, CC, MG, and SB, contributed by collecting data and revising the manuscript. GR was responsible for analyzing the data and writing the manuscript. EF, mentorship and revision of the manuscript.

FUNDING

This study was partially funded by the young investigator research fellowship by the Italian Society of Parenteral and Enteral Nutrition (SINPE, Società Italiana di Nutrizione Parenterale ed Enterale) for the project: "Valutazione nutrizionale nell'insufficienza renale mediante ecografia del muscolo quadricipite femorale" ("Nutritional assessment of patients with chronic kidney disease and acute kidney injury through ultrasound of the quadriceps femoris muscle") received by Alice Sabatino.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

The study was approved by the local Institutional Review Board (AVEN ref. no 45737, December 12th, 2015).

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41430-022-01166-7>.

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