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Original article

Handgrip strength is an independent predictor of all-cause mortality in maintenance dialysis patients

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SUMMARY

Background & aims: Muscle wasting is associated with mortality in dialysis patients. The measurement of muscle mass has some limitations, while muscle strength assessment is simple, safe and allows the recognition of patients at risk of progressing to poor outcomes related to malnutrition. The aim of this study is verify if handgrip strength (HGS) is associated with all-cause mortality in patients in maintenance haemodialysis (HD) and peritoneal dialysis (PD).

Methods: This was an observational retrospective cohort study which included all patients in maintenance HD and PD from July 2012 to October 2014. Patients were followed-up until June 2015.

Results: Two-hundred sixty five patients were enrolled (218 HD and 47 PD) and they were followed for 13.4 ± 7.9 months. During the follow-up period, 53 patients (20%) have died, 36 patients (13.6%) have undergone renal transplantation, 13 patients (4.9%) have switched off dialysis method and 5 patients (1.9%) have transferred to another facility. The cut-off of HGS able to predict mortality was 22.5 kg for men and 7 kg for women. Using this cut-off to fit the Kaplan–Meier survival curve, the association of HGS with all-cause mortality for both genders was confirmed. Finally, in the multivariate analysis adjusted for demographic, clinical and nutritional variables, HGS remained significant predictor of mortality, independent of dialysis modality.

Conclusions: HGS cut-offs that predict mortality were 22.5 kg for men and 7 kg for women. HGS was associated with mortality independent of dialysis modality.

1. Introduction

End-stage renal disease (ESRD) patients are at increased risk of protein energy wasting (PEW), which is characterized by muscle mass loss associated with inflammation [1]. Muscle mass wasting is highly prevalent among maintenance dialysis patients. Evidence of wasting can be noted in 18–75% of these patients, and it is an important predictor of morbidity and mortality [1]. Therefore, markers of muscle mass and muscle function could be important predictors of outcomes in this population [2–4].

Several methods have been used for determining muscle mass in dialysis patients, i.e., dual-energy X-ray absorptiometry, bioelectrical impedance analysis, and anthropometry. However, all of these methods have some relevant disadvantages [5,6]. In this context, handgrip strength (HGS) has gained considerable attention as an indicator of nutrition status and muscle function in recent research. HGS is a validated method to assess nutritional status [7]. It is fast, safe, simple, reliable, non-invasive, painless, radiation-free, and low cost [8]. It shows high inter-rater reliability and may be useful as an early indication of malnutrition [9]. Moreover, it seems not affected by hydration status [8,10], as the other methods for muscle mass assessment.

Studies with chronic kidney disease (CKD) patients have shown HGS is associated with malnutrition, assessed by Malnutrition Inflammation Score (MIS) [11] and renal outcomes (pre-dialysis mortality or reaching ESRD) [12]. In patients on maintenance

Abbreviations: ESRD, end-stage renal disease; PEW, protein energy wasting; HGS, handgrip strength; CKD, chronic kidney disease; HD, haemodialysis; PD, peritoneal dialysis; CRP, C – reactive protein; BMI, body mass index; MAMC, mid-arm muscle circumference.

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dialysis, HGS is associated with malnutrition evaluated by Subjective Global Assessment [13,14] and mortality [4,10].

In view of the simplicity and advantages of HGS assessment in evaluating nutritional status and the significant influence of muscle wasting on mortality of patients on dialysis, the aims of this study are: to determine a HGS cut-off for men and women and verify its association with mortality in patients on maintenance dialysis.

2. Materials and methods

2.1. Study design and subjects

It was a retrospective cohort study which included prevalent haemodialysis (HD) and peritoneal dialysis (PD) patients for at least three months, treated at Hospital of Botucatu Medical School from July 2012 to August 2014. Patients younger than 18 years and those with missing nutritional assessment data were excluded. Patients were evaluated and followed until death, transplantation, switch off dialysis method, transfer to another facility or the end of follow-up in June 2015. The study protocol was approved by local research ethics committee.

Following demographic, clinical and laboratory data were obtained from medical records: gender, age, dialysis vintage, main cause of ESRD, diabetes, serum urea, creatinine, albumin and C - reactive protein (CRP).

2.2. Assessment of nutritional status and muscle function

Anthropometric measurements were obtained from nutritional assessment performed after HD session or during routine outpatient care for PD patients. Body weight, height, mid-arm circumference and triceps skinfold thickness were measured. From these measurements, it was calculated body mass index (BMI), mid-arm muscle circumference (MAMC) and percent standard of MAMC was obtained from the National Health and Nutrition Examination Survey percentile distribution tables [15,16].

HGS was measured during nutritional assessment, using Jamar® mechanical dynamometer with a precision of 1 kg, in the dominant hand or in the non-fistula hand if implanted. Patients were instructed to self-adjust the dynamometer so that they fit comfortably to their hand size to get the best performance and to hold the grip with maximum force in response to a voice command, with the arm extended sideways from the body with the dynamometer facing away from the body. Three measurements were performed with intervals of about 30 s between each run and the maximum value was considered.

2.3. Statistical analyses

Data were expressed as mean ± standard deviation or median (first and third quartiles), and frequencies were expressed as percentage. Comparisons between genders and between survival and non-survival patients were performed using t Student's test or Mann Whitney. Frequencies were compared by qui-square test. Sensitivity and specificity analysis was performed to verify the best HGS cut-off able to predict mortality for men and women. A Receiver Operating Characteristic Curve Analysis (ROC curve) was constructed for each gender to verify the area under the curve and the significance of HGS on mortality prediction. Kaplan–Meier survival curves were fitted, and the difference between the curves was assessed by log-rank test. Cox proportional hazards analysis was used to assess independent predictors of mortality through models adjusted for variables significantly different between survival and non-survival patients. In this analysis, HG was included as a categorical variable according to the cut-off for each gender. Statistical significance was accepted as a p-value <0.05. Statistical analysis was performed using SPSS 22.0.

3. Results

3.1. Baseline characteristics

This study enrolled 265 patients on maintenance dialysis, most of them on HD (82.3%). Patients' age ranged from 18 to 91 years, and 54% were male. Diabetic nephropathy was the main cause of ESRD (31.1%), followed by hypertensive nephrosclerosis (18.1%). Patients mean BMI was 26.3 ± 7.1 kg/m^2 and mean HGS was 18.7 ± 11.2 kg. Mean HGS for men was 24 ± 11.6 kg and for women was 12.5 ± 6.7 kg ($p < 0.001$).

Demographic, clinical and nutritional data of entire cohort and according to gender is presented in Table 1.

Comparing patients according to dialysis methods, HD patients were majority male, with longer time of dialysis vintage and longer follow-up, and higher values of serum urea, creatinine and albumin ($p < 0.05$) than PD patients. HGS and frequency of outcomes were not different between HD and PD.

3.2. Comparisons between survival and non-survivals patients

Age, prevalence of diabetes, dialysis vintage and CRP were higher among non-survival patients, while serum urea, creatinine and albumin were higher among survival patients (Table 2).

3.3. Follow-up

Patients were followed-up for a mean 13.4 ± 7.9 months (minimum 0.6 and maximum 30.9 months). During this period, 53 patients (20%) have died, 36 patients (13.6%) have received renal transplantation, 13 patients (4.9%) have switched off dialysis method and 5 patients (1.9%) have been transferred to another facility.

3.4. ROC curve

According to ROC curves, HGS cut-off able to predict mortality were 22.5 kg for male, with 61% sensitivity and 76% specificity (AUC 0.689; CI 95% 0.575–0.803; $p < 0.003$) and 7 kg for female, with 83% sensitivity and 35.7% specificity (AUC 0.615; CI 95% 0.493–0.737; $p = 0.06$) (see Fig. 1).

3.5. Kaplan–Meier survival analysis

Survival probability analysis (Kaplan–Meier) confirmed the association of HGS with all-cause mortality for both gender (Fig. 2). The results showed statistical significance for both male (Fig. 2A) ($p = 0.003$) and female (Fig. 2 B) ($p = 0.004$).

3.6. Cox proportional hazards analysis

Models were fitted using cox proportional hazards analysis with HGS as a categorical variable, considering the cut-off for each gender (Table 3). First, crude analysis showed HGS as a significant predictor of mortality. HGS remained significant predictor of mortality even after adjustments.

4. Discussion

The present study showed HGS was able to identify increased risk of all-cause mortality in dialysis patients, with different cut-offs for genders. HGS is a measure widely used in clinical

Table 1
Baseline characteristics of 265 included patients and comparison between males and females.

Characteristic	Total (n = 265)	Men (n = 143)	Women (n = 122)	P
Age (years)	58 ± 15.2	59.2 ± 14.8	57.1 ± 14.5	0.7
Dialysis method [HD(%)/PD(%)]	218 (82.3)/47 (17.7)	124 (86.7)/19 (13.3)	94 (77)/28 (23)	0.04
Diabetes [n(%)]	122 (46.2)	62 (43.4)	60 (49.6)	0.31
Follow-up (months)	13.4 ± 7.9	13.8 ± 7.9	14.6 ± 8.3	0.88
Dialysis vintage (months)	14.3 (2.8; 36.7)	15.4 (3.9; 42.6)	19.4 (6.9; 40.6)	0.58
Cause of end-stage renal disease [n(%)]				
Diabetic nephropathy	83 (31.3)	46 (32.2)	37 (30.3)	0.49
Hypertensive nephrosclerosis	48 (18.1)	25 (17.5)	23 (18.9)	
Unknown	47 (17.7)	23 (16.1)	24 (19.7)	
Chronic glomerulonephritis	26 (9.8)	14 (9.8)	12 (9.8)	
ADPKD	8 (3.0)	7 (4.9)	1 (0.8)	
Other	53 (20.0)	28 (19.6)	25 (20.5)	
BMI (kg/m^2)	26.3 ± 7.1	25.3 ± 5.0	26.5 ± 6.2	0.02
Percent standard of MAMC (%)	99.7 ± 16.8	91.8 ± 11.4	109.3 ± 18.0	<0.01
Handgrip strength (kg)	18.7 ± 11.2	24.0 ± 11.4	12.5 ± 6.5	<0.01
Serum urea (mg/dl)	104.6 ± 34	111.1 ± 34.6	101.9 ± 32.5	0.01
Serum creatinine (mg/dl)	8.5 ± 3	9.2 ± 2.9	8.1 ± 2.7	<0.01
Serum albumin (g/dl)	3.8 ± 0.5	3.9 ± 0.5	3.8 ± 0.6	0.22
C reactive protein (mg/dl)	1 (0.5–1.9)	1.1 (0.5; 1.9)	0.9 (0.5; 1.8)	0.97
Haemoglobin (g/dl)	11.1 ± 1.8	11.57 ± 1.8	11.21 ± 1.6	0.10
Serum bicarbonate (mEq/L)	22.4 ± 2.8	22.39 ± 2.8	22.53 ± 3.0	0.70
Kt/V	1.5 ± 0.4	1.4 ± 0.3	1.7 ± 0.5	<0.01

Abbreviations: HD: haemodialysis; PD: peritoneal dialysis; ADPKD: autosomal dominant polycystic kidney disease; BMI: body mass index; MAMC: mid-arm muscle circumference.
Percent standard of MAMC was obtained from the National Health and Nutrition Examination Survey percentile distribution tables [15].

practice, due to its ability to easily suggest protein energy malnutrition. Moreover, it is simple, fast, non-invasive, and represents a reliable malnutrition marker [8,9]. Malnutrition has been independently associated with poor outcomes, such as hospitalization, longer length of hospital stay and mortality [17]. Studies have shown HGS as a good nutritional status indicator, able to diagnose early malnutrition due to changes in muscle function [7–9,18].

There is a lack of consensus on HGS reference values for patients on dialysis, as well on the methodology to measure HGS. Leal et al. showed in a systematic review that dialysis patients HGS values range from 12 to 38 kg for men and from 12 to 26 kg for women [19]. The mean HGS found in the present study meets this finding. It was 24 kg for men and 12.5 kg for women.

Matos et al. [4] showed values 28.3 kg for men and 21.5 kg for women were the best cut-offs to predict mortality in haemodialysis patients. In this study, the values were lower and more disparate: 22.5 kg for men and 7 kg for women. This result was expected, because gender is already well known as an important determinant of HGS [20].

As well as gender, age is another factor that influences muscle strength [20–22]. Uraemic phenotype is known to be characterized by premature ageing, which accelerates characteristics as

Table 2
Comparison between demographic, clinical and nutritional characteristics of survivals and non-survivals patients.

Characteristic	Survival (n = 212)	Non-survival (n = 53)	P
Age (years)	57 ± 15.5	62.9 ± 13	<0.01
Gender [Male(%)]	118 (55.7)	25 (47.2)	0.27
Dialysis method (HD/PD)	171 (80.7)/41 (19.3)	47 (88.7)/6 (11.3)	0.17
Diabetes [n(%)]	91 (42.9)	31 (59.6)	0.03
Follow-up (months)	13.8 ± 7.9	11.7 ± 7.5	0.08
Dialysis vintage (months)	11.8 (2.4; 34.9)	26.3 (9.1; 56.6)	<0.01
Cause of end-stage renal disease [n(%)]			
Diabetic nephropathy	63 (29.7)	20 (37.7)	0.65
Hypertensive nephrosclerosis	37 (17.5)	11 (20.8)	
Unknown	41 (19.3)	6 (11.3)	
Chronic glomerulonephritis	22 (10.4)	4 (7.5)	
ADPKD	7 (3.3)	1 (1.9)	
Other	42 (19.8)	11 (20.8)	
BMI (kg/m^2)	26.3 ± 7.1	26.2 ± 6.9	0.94
Percent standard of MAMC (%)	99.6 ± 16.3	99.8 ± 18.8	0.96
Handgrip strength (kg)	19.9 ± 11.3	13.6 ± 9.6	<0.01
Serum urea (mg/dl)	106.6 ± 34.2	96.4 ± 31.6	0.05
Serum creatinine (mg/dl)	8.7 ± 3.1	7.8 ± 2.5	0.05
Serum albumin (g/dl)	3.8 ± 0.5	3.7 ± 0.5	0.06
C reactive protein (mg/dl)	0.9 (0.5; 1.8)	1.5 (0.7; 2.2)	0.01
Haemoglobin (g/dl)	11.4 ± 1.8	11.2 ± 1.5	0.37
Serum bicarbonate (mEq/L)	22.3 ± 2.7	22.9 ± 3.5	0.16
Kt/V	1.5 ± 0.4	1.5 ± 0.4	0.93

Abbreviations: HD: haemodialysis; PD: peritoneal dialysis; ADPKD: autosomal dominant polycystic kidney disease; BMI: body mass index; MAMC: mid-arm muscle circumference.

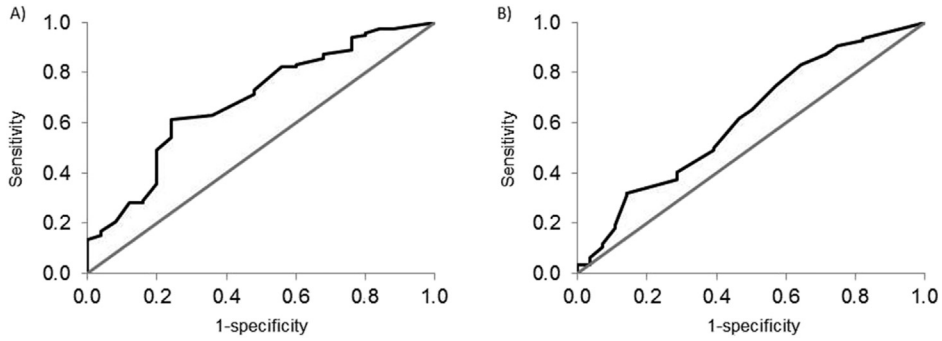

Fig. 1. ROC curves showing prediction of mortality by handgrip strength (A) for men and (B) for women.

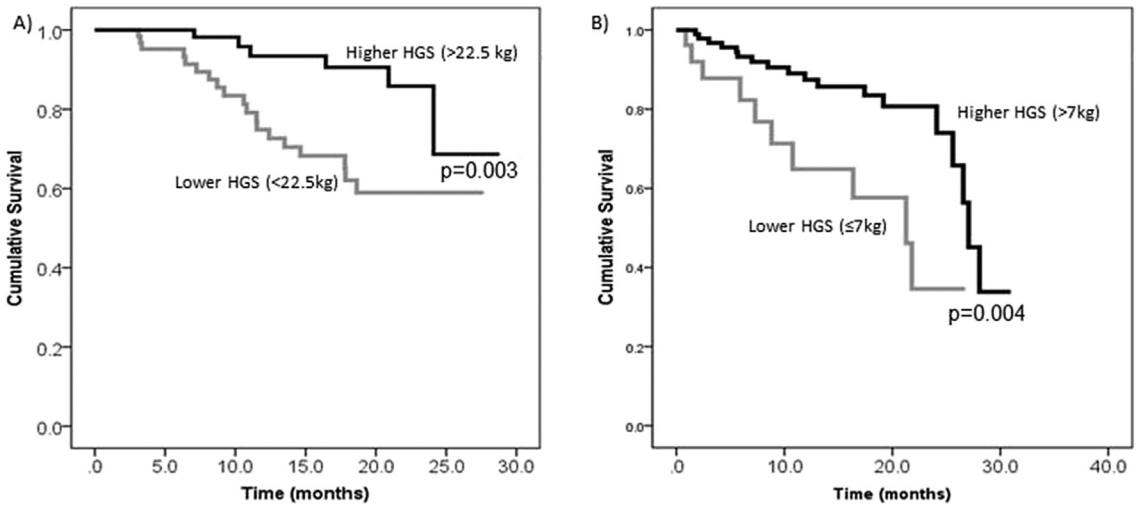

Fig. 2. Kaplan–Meier survival analysis of handgrip strength (A) for men and (B) for women.

osteoporosis, atherosclerosis, frailty and muscle wasting [23]. Therefore, there is a disconnection between calendar age and biological age in CKD that affects the muscle of these patients [24]. Nutritional status, which is usually reduced in chronic diseases, also exerts a substantial impact on muscle strength [7,12,25]. Other factors are associated with chronic diseases and contributes to muscle weakness as well: disease severity, comorbidities, medical treatment, and immobilisation [7].

Clinical and biochemical characteristics (age, diabetes, dialysis vintage, serum albumin, creatinine, urea and CRP) were different between survival and non-survival groups. These variables are associated with comorbidities, inflammation and nutritional status, therefore they can influence muscle strength. However, after multivariate analysis which included these variables, only HGS remains associated with mortality.

Table 3
Cox Proportional Hazard Analysis for evaluating the impact of handgrip strength on all-cause mortality in dialysis patients.

		HR (95% CI)	P
Crude		0.37 (0.21-0.64)	<0.01
Model 1	Age	1.01 (0.99–1.03)	0.46
	Dialysis vintage	1.01 (0.99–1.01)	0.12
	Diabetes	1.6 (0.88–2.88)	0.12
	C reactive protein	1.05 (0.99–1.1)	0.06
	Serum creatinine	0.88 (0.78–0.99)	0.047
	Handgrip strength	0.49 (0.27–0.89)	0.019

Handgrip strength is a categorical variable according to the cut-off for each gender.

Muscle mass assessed by MAMC wasn't significantly different between survival and non-survival groups. On the other hand, muscle function assessed by HGS was statistically different between these groups. Isoyama et al. [3] showed decreased muscle strength was more strongly associated with mortality than decreased muscle mass in patients on dialysis. Therefore, muscle mass loss and muscle strength loss seems not to occur simultaneously.

Many studies have shown the prediction of low muscle mass in mortality in patients on dialysis [26–28]. As the decrease of muscle strength may occur before the decrease of muscle mass, it seems prudent to suggest that treatment options in dialysis patients should target not only maintenance or increase of muscle mass but also muscle functionality [3].

This study had some methodological limitations. Sample size was from a single centre, and longitudinal changes in HGS measurements were not assessed during follow-up. Because this is an observational study, there are confounding factors in the prediction of mortality. Despite these limitations, this study showed an association between HGS and mortality, independent of dialysis modality and other characteristics usually associated with poor outcomes.

In conclusion, HGS is an independent predictor of all-cause mortality in patients on maintenance dialysis. HGS cut-offs that predicted mortality were 22.5 kg for men and 7 kg for women. HGS

was associated with mortality independent of dialysis modality. Moreover, measurement of HGS can be useful in clinical practice. It is noteworthy that the results of this study are significant and may base robust studies with longitudinal assessments to evaluate the influence of changes in muscle strength and mortality risk.

Statement of authorship

B. P. Vogt and M. C. C. Borges contributed to the conception and design of the research; B. P. Vogt, M. C. C. Borges C. R. Goes, and J. C. T. Caramori contributed to the acquisition, analysis, or interpretation of the data; B. P. Vogt and M. C. C. Borges drafted the manuscript; B. P. Vogt, M. C. C. Borges, C. R. Goes and J. C. T. Caramori critically revised the manuscript; and B. P. Vogt, M. C. C. Borges, C. R. Goes and J. C. T. Caramori agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

Conflict of interest

The authors declare they have no conflicts of interest.

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