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Combined use of handgrip strength and hemoglobin as markers of undernutrition in patients with stage 3–5 chronic kidney disease☆

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Abstract *Background and aims:* The early identification of undernourished patients with CKD could help instating appropriate nutritional intervention before the full development of the threatening condition known as Protein Energy Wasting (PEW). Handgrip strength (HGS) and blood hemoglobin (Hb) concentration are two parameters considered representative of nutritional status but not included among the criteria for PEW diagnosis. In the present work we investigated whether they could help identifying CKD patients at risk of undernutrition.
Methods and results: We performed a two-step cluster analysis to classify a cohort of 71 stage 3–5 CKD patients, none of which with PEW, according to their Hb concentration and dominant-hand HGS. Two clusters were finely separated using this method. When we compared the two groups for main body composition and nutritional variables by using t-test statistics or Mann–Whitney test, as appropriate, we found significant differences in PhA, ECW/TBW, ASMI, serum iron. Then we stratified our population by gender and performed cluster analysis as well. PhA, ECW/TBW were still significantly different in the two clusters both in M and in F, while serum iron concentration only in males and ASMI only in females.
Conclusion: These results suggest that either in male than in female Hb concentration and HGS may distinguish two subgroups of CKD patients with different nutritional status and disease severity. Patient belonging to either of these cluster can be easily identified by using the HGS/Hb ratio which represents the HGS normalized per gr Hb.

1. Introduction

Malnutrition and muscle mass loss occur frequently in chronic kidney disease (CKD) [1] and are associated to a bad prognosis [2–4]. These phenomena may progress to a serious condition known as protein energy wasting (PEW), which has been defined by a panel of expert of the International Society of Renal Nutrition and Metabolism (ISRNM) as the *loss of body protein mass and fuel reserves (that is, body protein and fat masses)* [5]. PEW has a complex pathophysiology and both increased catabolism and reduced nutrient intake contribute to its genesis [6]. The appearance of PEW has an ominous impact on CKD and every effort should be done to prevent its development by the early establishment of a specific nutritional and physical exercise program.

According to the consensus published by ISRNM panellists, PEW diagnosis is established when at least three of

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the following criteria are met: 1) serum albumin <3.8 g/dL (or, alternatively, prealbumin <30 mg/dL or cholesterol <100 mg/dL); 2) body mass index (BMI) < 23 kg/m^2 or total body fat mass <10% or an unintentional weight loss over time (5% over 3 months or 10% over 6 months); 3) a decrease in muscle mass (>5% in 3 months or >10% in 6 months) or a reduced mid-arm muscle circumference area (reduction >10% in relation to 50th percentile of reference population) or creatinine appearance and 4) an unintentional low dietary protein intake (DPI) < 0.80 g kg^{-1} day^{-1} for at least 2 months for dialysis patients or <0.6 g kg^{-1} day^{-1} for patients with CKD stages 2–5 or an unintentional low dietary energy intake (DEI) < 25 kcal kg^{-1} day^{-1} for at least 2 months [5]. However, several problems may complicate the use in clinical practice of these diagnostic criteria. For instance, fluid retention, which frequently occurs in patients with advanced CKD, may obscure the loss of lean mass, and, in patients suffering from obesity and CKD, fat accumulation may have similar effects ultimately leading to the non-recognition of PEW. Likewise, serum albumin concentration may be affected by factors other than PEW such as age, sex, comorbidities, fluid overload or low-grade chronic inflammation and this complicates its interpretation in the process of PEW diagnosis [7]. A further major problem for the diagnosis of PEW is that, in order to demonstrate loss of muscle mass (MM) over time, it must be measured at different time points either by bioelectrical impedance analysis (BIA), computed tomography (CT) or dual-energy X-ray absorptiometry (DEXA); the latter may sometimes not be feasible in routine clinical practice given the poor accessibility and high cost of these procedures and, even when it can be done, may result in a significant delay in diagnosis [8]. Therefore, in 2014 Moreau-Gaudry et al. [9] suggested that serum creatinine adjusted for body surface area (sCr/BSA) could be used in the place of the measurement of muscle mass change over time in order to make PEW diagnosis easier and not depending on a long patient follow-up.

The diagnostic criteria for PEW are stringent and only apply to patients at an advanced stage of wasting. However, progression to PEW is gradual and identifying milder alterations in nutritional status and body composition could help identifying patients that may benefit of early nutritional treatment to prevent PEW. Different criteria could be used to intercept early stages of undernutrition. The Consensus Statement from the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) for the identification of adult malnutrition makes a distinction between *nonsevere (moderate) malnutrition* and *severe malnutrition* based on six evidence-based criteria: insufficient energy intake, weight loss, muscle mass loss, subcutaneous fat loss, fluid accumulation and diminished "functional status" as measured by handgrip strength (HGS) [10].

Low HGS has not been considered among the criteria for PEW diagnosis even though its correlation with functional disability and the risk of mortality in CKD has been well established [11,12]. In addition, in non-dialysis CKD patients, HGS has a strong negative correlation with the malnutrition/inflammation score [13], whereas it positively correlates with lean mass and plasma proteins [14] has been reported. The observed good correlation between HGS and nutritional status can be easily explained considering that muscle function does not only depend on muscle mass but also on nutrient availability [15]. Importantly, a decrease in HGS may occur quite early in CKD progression and can be observed already in KDOQI stage III, well before PEW fully develops [16]. Collectively, these observations suggest that HGS measurement could represent a valuable tool to identify early stages in the progression of malnutrition and wasting in CKD.

Furthermore, malnutrition is a common cause of anemia, the so-called nutritional anaemia (ICD-10 D53.9). Although not included in current diagnostic criteria for this condition, anaemia, as indicated by low hemoglobin concentration, is an indicator of malnutrition especially in certain clinical conditions such as old age [17,18]. In CKD, anaemia has a much more complex pathophysiology than *pure* nutritional anaemia, being contributed for by additional factors besides malnutrition, which include decreased erythropoietin (EPO) synthesis and release, increased circulating levels of proinflammatory cytokines and disturbed iron metabolism [19]. It is well established that the presence of anaemia in patients with CKD is associated with poorer quality of life, i.e. functional impairment, impaired mobility, increased risk of falls [20] and increased risks of adverse clinical outcomes [21]. Patients with lower Hb levels are also those with a worse nutritional status and PEW is a predictor of poor responsiveness to treatment with exogenous EPO in HD patients [22]. Therefore, low Hb values in CKD patients are an indirect index of disease severity which also includes the impairment of nutritional status. Importantly, according to the NADIR-3 study, Hb levels may start to decrease already in stage III KDOQI and anaemia progressively worsen with disease progression [23].

The evidence that Hb starts decreasing well before the development of PEW suggests that it could be useful to identify early stages of malnutrition and wasting in CKD.

Based on these considerations, in the present study we investigated whether HGS or Hb levels could be used to identify, in CKD patients, a moderate impairment of their nutritional status and muscle mass which does not yet meet the PEW diagnostic criteria but could represent an early stage in the development of this condition. Since both Hb concentration [24] and HGS [25] show a significant gender dimorphism being higher in males than in females, data from the two genders were examined independently.

2. Methods

2.1. Study design and inclusion and exclusion criteria

The present investigation was a single-centre retrospective observational study based on the analysis of the medical records of CKD patients who came for consultation at the Outpatient Clinic of Nutrition in CKD and Transplantation,

of our institution from January to November, 2019. The medical records collected at our consultation service routinely include anthropometric and laboratory data, data on body composition assessed with BIA and HGS measurement. These data were used to assess by cluster analysis whether HGS or Hb segregate patients with maintained or with early impairment of the nutritional status or muscle mass. This study protocol was approved by the Ethics Committee of the School of Medicine of the Federico II University of Naples (protocol number 181/18); procedures were performed according to the World Medical Association Helsinki Declaration as revised in 1996.

Inclusion criteria were: age higher than 18 and lower than 70 and KDOQI stages 3–5 CKD, with no limitation on gender or BMI. Exclusion criteria were: pregnancy or puerperium; the presence of PEW; previous kidney transplantation; renal replacement treatment (both haemodialysis and peritoneal dialysis); exogenous erythropoietin and/or iron therapy during the 6 months before the first visit at our outpatient clinic, major cardiovascular events or severe infection in the three months preceding the outpatient visit; HIV; muscle dystrophy and other muscle disorders either primary or caused by neurological diseases; metastatic cancer treated with chemotherapy, immunotherapy or radiotherapy; enteral or parenteral nutrition; autoimmune diseases treated with corticosteroids or other immunosuppressant drugs; liver failure.

2.2. Anthropometry and body composition analysis

Height and weight were determined with a calibrated stadiometer and scale. Body mass index (BMI) was defined as the weight in kilograms divided by squared height (in meters) [26].

Body composition was determined by conventional bioelectrical impedance analysis (BIA). Resistance (R) and Reactance (Xc) were measured with a single-frequency 50 kHz bioelectrical impedance analyzer (BIA 101 RJL, Akern Bioresearch, Firenze, Italy) according to the standard tetrapolar technique by applying the software provided by the manufacturer, which incorporated validated predictive equations for total body water (TBW), fat mass (FM) and fat free mass (FFM) [27–29]. Phase Angle (PhA) was extrapolated from the values of reactance and resistance as well.

All enrolled subjects had previously been instructed to fast (also avoiding coffee consumption) or avoid physical activity before taking this test.

Estimated Appendicular Skeletal Muscle mass (ASM) was calculated using the Kyle prediction equation [30]:

$$ASM(kg) = -4.211 + \left(0.267 \times \frac{Ht^2}{R}\right) + (0.095 \times weight) + (1.909 \times gender) + (-0.012 \times age) + (0.058 \times X)$$

where gender = 1 for men and 0 for women.

ASM was normalized to height and expressed as appendicular muscle/height^2 (ASMI).

2.3. HGS measurement

Hand grip strength (HGS) was measured to the nearest kilogram using a hand dynamometer on the dominant hand (78,010; Lafayette Instrument Company, Lafayette, IN, USA). Measurement was performed while keeping the patient in an upright position with the arms unsupported and parallel to the body. The average of three consecutive measurements obtained with 30 s rest was used for the analysis.

2.4. Nutritional assessment

Food intake data were obtained using specific weekly Food Frequency Questionnaires (FFQ) that record the frequency with which an individual consumes food and beverages, listed collectively (e.g. vegetables) or individually (e.g. eggs), including questions about the usual amount consumed, over 7 days. Thus, the average weekly caloric intake for each patient was calculated.

A trained dietician also carried out a 24-HDR (24 h dietary recall), i.e. an interview concerning food and drinks consumed during the day preceding the outpatient visit [31].

2.5. Blood chemistry

Blood chemistry analysis was performed with routine laboratory methods and included urea nitrogen, creatinine, albumin, hemoglobin, total cholesterol, triglycerides and glucose. In all patients, estimated Glomerular Filtration Rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [32].

2.6. Statistical analysis

Statistical analysis was performed using IBM SPSS 20.0 for Windows (Armonk, NY, USA) and the free statistic software Jamovi version 2.2.5.0 (https://www.jamovi.org/). Data were examined for normality with the Shapiro–Wilk test and presented as mean ± SEM if normally distributed and as median with interquartile range (IQR), if not. Two-group comparisons were performed using t test, or Mann Whitney U test as appropriate. Data were partitioned in clusters using the K means clustering method and HGS measure and Hb blood concentration as clustering variables. Data in the two clusters were then compared by unpaired Students' t Test or Mann Whitney U test as appropriate. Receiver Operating Characteristic (ROC) curve analysis was performed to assess whether the HGS/Hb ratio could be used to predict whether a specific patient belonged to cluster 1 or 2.

3. Results

3.1. Study population

Study population consisted of 47 male and 24 female adult patients with clinically stable stage 3–5 CKD. The mean age was 60 [50–68] and 57 [41.3–68.5] years in males and

Table 1 Anthropometric characteristics and selected parameters of nutritional status in patients with CKD stages 3–5.

	ALL (n = 71)	MALE (n = 47)	FEMALE (n = 24)
Age (years)	59 [48–68]	60 [50–68]	57 [41.3–68.5]
BW (kg)	75.2 ± 17.6	81.1 ± 16.4	63.5 ± 13.7*
BMI (BW/H^2)	26.4 [23.4–30.7]	26.7 [24.2–30.7]	25.6 [22.7–30.3]
Diabetes (%)	21.1	23.4	16.7
CKD vintage. (months)	92.2 ± 100.2	88.1 ± 71.4	99.6 ± 141.0
CKD stage			
Stage 3 (%)	49.3	59.6	29.2
Stage 4 (%)	28.2	21.3	41.7
Stage 5 (%)	22.5	19.1	29.2
Albumin (g/dl)	4.1 [3.9–4.5]	4.1 [4.0–4.5]	4.1 [3.9–4.4]
Hemoglobin (g/dl)	12.8 [11.6–14.3]	13.6 [12.0–14.8]	11.8 [10.6–12.5]
Blood glucose (mg/dL)	86.5 [78.8–106.3]	90.0 [83.0–107.0]	82.0 [71.0–106]
Cholesterol (mg/dl)	114.0 [89.0–167.3]	172.5 [143.8–195.8]	179 [164.3–204.3]
HDL-Cholesterol (mg/dl)	45.8 ± 12.1	41.4 ± 10.5	54.0 ± 10.6
Triglycerides (mg/dl)	114.0 [89.0–167.3]	143.0 ± 81.5	121.4 ± 51.5
BUN (mg/dl)	62.0 [48.0–108.0]	62.0 [48.0–89.0]	69.5 [49.3–115.5]
Creatinine (mg/dl)	2.1 [1.5–3.2]	2.1 [1.5–3.2]	2.4 [1.5–4,2]
eGFR (ml/m × 1.73 m^2)	29.0 [18.0–45.0]	34 [19–46]	21 [10.8–37.8]
FFM (% BW)	72.0 ± 8.8	74.6 ± 7.7	66.8 ± 8.5*
FM (% BW)	28.9 ± 9.2	26.4 ± 8.4	33.8 ± 8.9*
ECW/TBW	47.3 ± 6.1	45.6 ± 5.4	51.0 ± 6.1*
Phase angle (°)	5.8 ± 1.2	6.1 ± 1.2	5.2 ± 1.0*
ASMI (kg/m^2)	7.9 ± 1.5	8.6 ± 1.2	6.4 ± 1.1*
Hand grip (kg)	28.5 ± 9.6	33.5 ± 7.2	18.8 ± 5.3*
Total calories in diet (kcal/day)	1925,3 ± 411.8	2062.1 ± 390.8	1662.9 ± 317.2*
Total proteins in diet (g/day)	0.75 [0.6–0.9]	0.8 [0.6–0.9]	0.7 [0.6–0.9]

*$p < 0.05$ vs male.
ASMI, ASM/h^2; BMI, body mass index; BUN, blood urea nitrogen; BW, body weight; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FFM, fat free mass; FM, fat mass; ECW, extracellular water.

females, respectively. BMI was 26.7 [24.2–30.7] kg/m^2 in males and 25.6 [22.7–30.3] kg/m^2 in females. The main laboratory and body composition characteristics of the patients are summarized in Table 1. As per inclusion criteria, none of the patients complied with the criteria for PEW diagnosis. Serum albumin was lower than 3.8 g/dL only in 8 patients (5 males), BMI was lower than 23 in 16 (7 males), total body fat mass <10% only in one (male) patient, and no patients showed a sCr/BSA ratio lower than 380 μmol/L/m^2 (i.e. the thresholds for PEW diagnosis according to Fouque and Moreau-Gaudry [5,9]). HGS was lower than the threshold value for sarcopenia diagnosis (27 and 16 Kg respectively in males and females [33]) in 6 males (12.8%) and 5 females (20.8%).

3.2. Cluster analysis of the study population

We performed cluster analysis, using dominant hand HGS and Hb concentration as discriminants, to partition the study population in clusters with high within-cluster homogeneity and between-cluster heterogeneity. By using this approach two clusters were clearly separated, the first one (cluster 1 consisting of 31 males and 2 females) with centroid at 0.766 and 0.746 HGS and Hb z-scores (high HGS and high Hb), and the second one (cluster 2, consisting of 16 males and 22 females) at −0.745 HGS z-score and −0.725 Hb z-score (low HGS and low Hb), respectively.

These two clusters differed in key nutritional and body composition parameters. In fact, patients in cluster 1 had higher waist circumference (102.2 ± 17.8 vs 91.8 ± 12.8 cm, $p < 0.01$), ASMI (8.6 ± 1.3 vs 7.2 ± 1.4 kg/m^2, $p < 0.001$), PhA (6.3 ± 1.2 vs 5.3 ± 1.0°, $p < 0.001$), daily calory intake (2062.7 ± 391.2 vs 1809.5 ± 397.4 Kcal/day, $p < 0.01$), serum iron concentration (92.0 [70.5–112.0] vs 61.0 [49.0–78.0] μg/dL, $p < 0.001$), and, obviously, HGS (36.0 ± 6.0 vs 22.0 ± 7.0 Kg, $p < 0.001$) and Hb concentration (14.4 [13.6–15.2 vs 11.8 [10.6–12.4] g/dL, $p < 0.001$). On the contrary, patients in cluster 2 showed higher creatinine concentrations (2.37 [1.78–4.8] vs 1.69 [1.45–2.48] mg/dL, $p < 0.05$), ECW% (49.7 ± 5.8 vs 44.6 ± 4.9, $p < 0.001$) and ECW/TBW ratio (0.5 ± 0.06 vs 0.45 ± 0.05, $p < 0.001$). No difference was observed between cluster 1 and 2 neither in age (cluster 1: 60.5 [49.5–68]; cluster 2: 58 [46–67]) or in eGFR (cluster 1: 33.5 [18–33.5]; cluster 2: 24 [15.5–45.5]).

These results, however, could be biased by the different number of males and females in the two clusters. Therefore, to avoid gender-related biases, we stratified our patient population in males and females and performed cluster analysis separately in the two genders. As shown in Fig. 1, two clusters were nicely separated both in males and in females. In males, cluster centroids were at 0.5347 HGS and 0.4959 Hb z-scores for cluster 1, and at −0.7989 HGS- and −0.8614 and Hb z-scores for cluster 2. In females, cluster 1 showed the centroids at 0.6544 HGS- and 0.5352 Hb z-scores and cluster 2 at −0.9162 HGS- and −0.7492 Hb z-scores.

Both in males and in females, significant differences were observed when cluster 1 and cluster 2 were

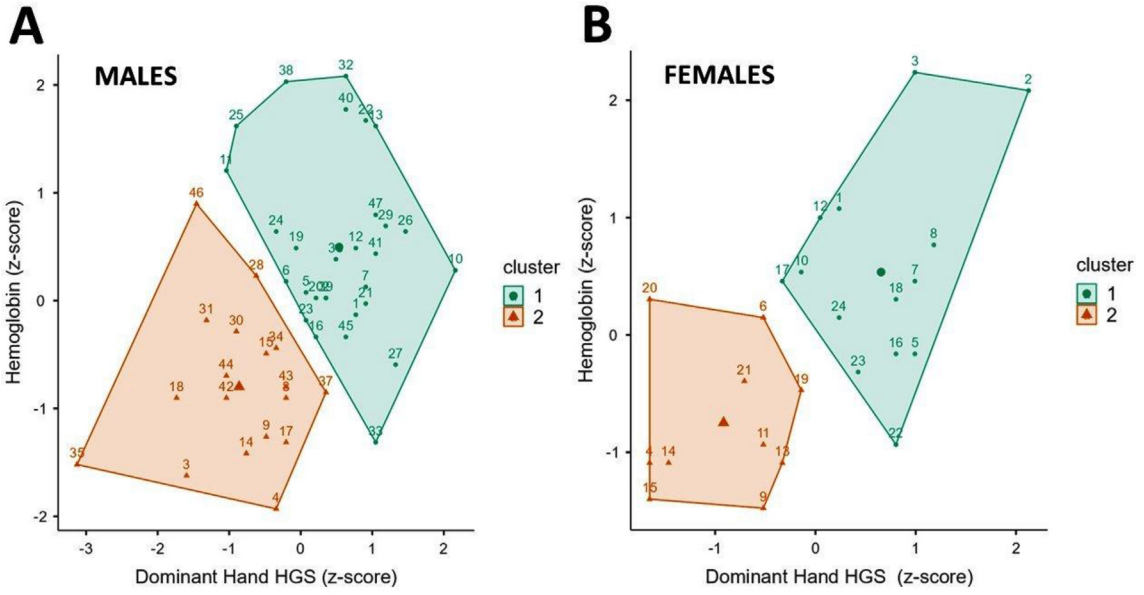

Figure 1 Data clusters identified by HGS and Haemoglobin concentration in males (A) and in females (B).

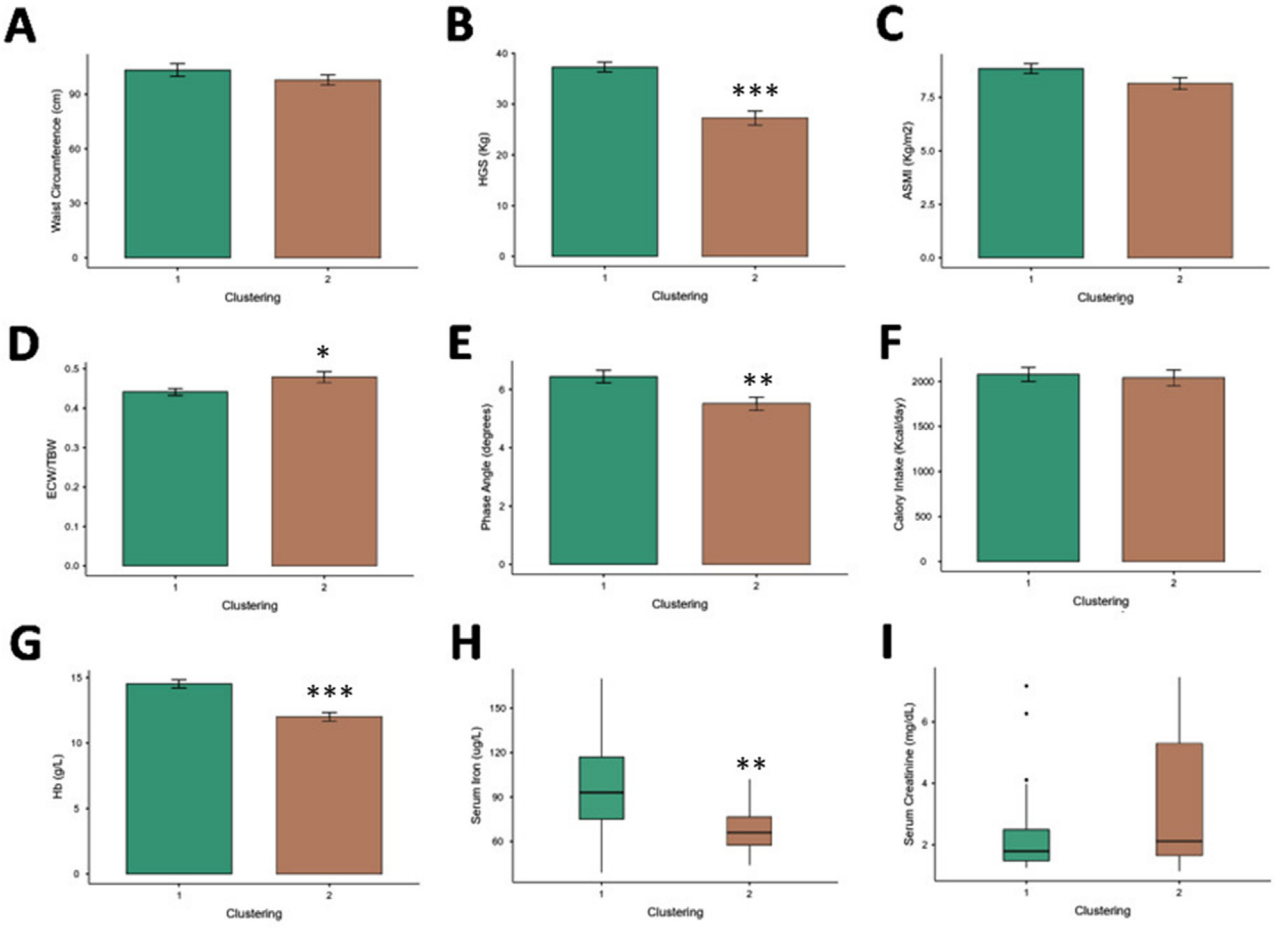

Figure 2 Nutritional and body composition parameters in men belonging to clusters 1 and 2. A. waist circumference, B. HGS, C. ASMI, D. ECW/TBW, E. Phase Angle, F. Daily Calory Intake, G. Hb concentration, H. Serum Iron, I. Serum creatinine. *, $p < 0.05$; ***, $p < 0.01$; ***, $p < 0.001$.

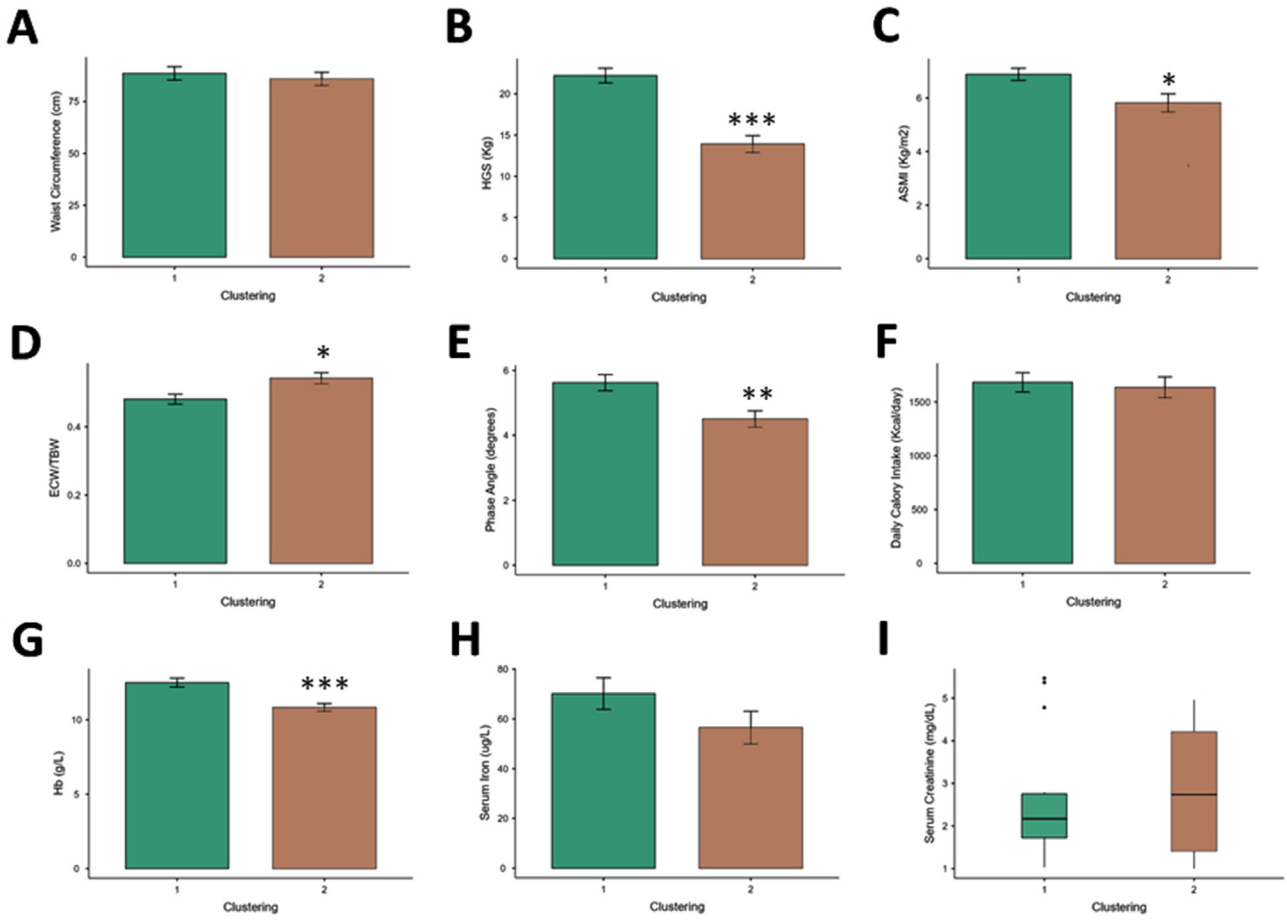

Figure 3 Nutritional and body composition parameters in women belonging to clusters 1 and 2. A. waist circumference, B. HGS, C. ASMI, D. ECW/TBW, E. Phase Angle, F. Daily Calory Intake, G. Hb concentration, H. Serum Iron, I. Serum creatinine. *, $p < 0.05$; ***, $p < 0.01$; ***, $p < 0.001$.

compared for key nutritional and body composition parameters (Figs. 2 and 3). Specifically, PhA and ECW/TBW were significantly different in the two clusters both in males (PhA: 6,4 ± 1.1 vs 5.5 ± 1.0; ECW/TBW: 0.4 ± 0.04 vs 0.5 ± 0.05) and in females (PhA: 5.6 ± 0.9 vs 4.5 ± 0.8, $p < 0.05$; ECW/TBW: 0.48 ± 0.06 vs 0.54 ± 0.05, $p < 0.05$). By contrast, serum iron concentration was higher in cluster 1 than in cluster 2 only in males (94.7 ± 29.7 vs 68.5 ± 16.7, $p < 0.05$) but not in females and ASMI in females (6.9 ± 0.9 vs 5.8 ± 1.0, $p < 0.05$) but not in males. No significant difference was observed in caloric intake in either gender.

3.3. ROC curve analysis using the HGS/Hb ratio as a predictor

Since the results that we reported in the previous sections showed that HGS and Hb concentration separate two different clusters of patients with CKD, we were interested in identifying a single numeric parameter that could predict whether a given patient belongs to either cluster 1 or cluster 2. To test whether the HGS/Hb ratio (i.e., normalized grip strength per gr of Hb) could be such a parameter we used ROC analysis. The area under the curve was 0.769 ± 0.057 ($p = 1.98501e{-}06$) (Fig. 4). The optimal cut-

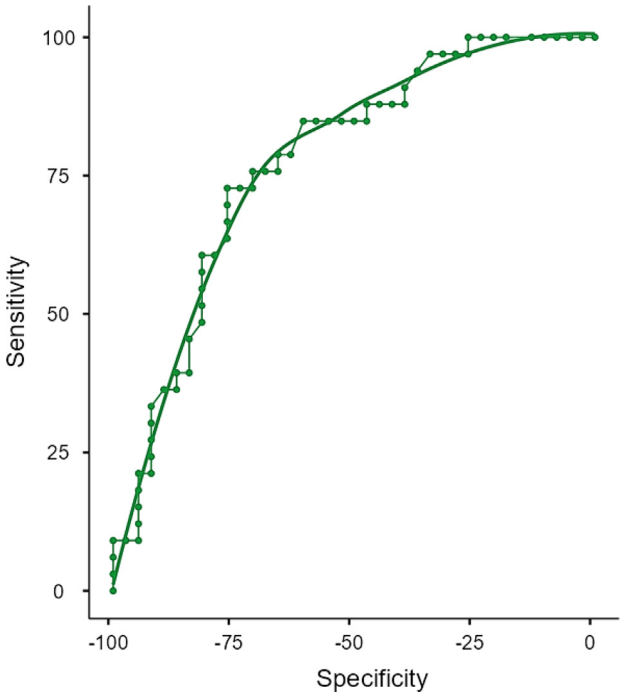

Figure 4 ROC curve showing the specificity and sensitivity of the HGS/Hb ratio in distinguishing between cluster 1 and cluster 2 patients. Both raw data and the fitted curve are shown in the figure.

off values estimated from the Youden Index was 2.24 which corresponds to the value that discriminates cluster 2 from cluster 1 with a specificity and a sensitivity respectively of 0.763 and 0.719.

4. Discussion

In the present paper we showed that the combined use of HGS and Hb measurement is effective in segregating CKD patients with no PEW in two subgroups: those with higher muscle mass and better nutritional status and those with lower muscle mass and worse nutritional status.

Identifying patients with initial derangement of the nutritional status and muscle mass could have clinically relevant implications since it could help implementing nutritional and physical activity interventions aimed to slow the progression towards PEW. PEW is, indeed, a dangerous complication of late CKD which has a major role in determining the bad progression of the disease and whose development should be, therefore, strongly counteracted. However, accomplishing this task appears complicated. Measuring body weight or BMI does not help so much since the loss of muscle mass, which frequently occurs in CKD patients because of multiple factors including metabolic acidosis, appetite suppression, insulin resistance and inflammation [34,35], may be counterbalanced by the concurrent increase in fat mass and extracellular fluid [6]. Therefore, alternative approaches are needed. By using cluster analysis, in the present study we evaluated whether HGS and Hb measurement could be helpful to achieve this goal.

The first parameter that we used in our study was HGS measurement. This test essentially evaluates muscle strength which makes it highly suitable as a screening tool for our purposes. In fact, muscle strength depends on multiple parameters including not only muscle mass, but also muscle quality (i.e. the kind of fibers that compose the tested muscles and the presence of intramuscolar fatty infiltration) and it is extremely sensitive to nutrient and oxygen availability [36]. As a matter of fact, previous studies showed already that HGS measurement correlates with nutritional status not only in several clinical settings including hospitalized patients from medical or surgical wards [37,38] or community-dwelling older adults [39] but also in the whole (apparently healthy) US population [40]. Remarkably, muscle strength declines rapidly in response to nutrient deprivation and, therefore, HGS measurement is considered a reliable tool for the early detection of impending malnutrition and the selection of patients that could benefit of early nutritional support [39,41]. The potential application of HGS measurement as a nutritional index in renal failure has been investigated already in previous studies that showed, for instance, its strong correlation with nutritional status in patients with ESRD starting dialysis [14] and in non-dialysis stage 2–5 CKD patients [13]. A major advantage of using HGS measurement is that this is a cheap and widely available test that is highly suitable for rapid patient screening in outpatient settings.

The second parameter that we used for cluster discrimination was Hb concentration in blood. The ability of low Hb to segregate patients with poor nutritional status and muscle mass from those with better general conditions can be explained considering that, in CKD, anaemia is multifactorial in origin. In particular, poor nutrition and, especially, iron deficiency are among the most important causative factors together with a decrease in endogenous EPO production, and inflammation with increased hepcidin levels [42]. Not only low Hb is related to poor nutrition but it can also directly contribute to decrease skeletal muscle mass and strength as a consequence of reduced oxygen delivery to skeletal muscle [43], and this negatively affects muscle mass and strength [44–47].

By the combined use of HGS and Hb we were successful in separating our CKD patient population in two groups, the one with a better and the other with a worse nutritional and body composition status. Importantly, gender-related differences exist in both Hb concentration [24] and HGS [25]. Therefore, to avoid biases deriving from the different number of males and females in our study population we performed cluster analysis separately in the two genders. The results obtained after stratifying patients according to their gender, showed, once again, that by the combined use of HGS and Hb two clusters can be separated in both males and females, the first characterized by a better nutritional and body composition status than the other one. In fact, both males and in females patients in cluster 1 (high HGS and Hb) had higher PhA and lower ECW% and ECW/TBW values than those of cluster 2. A wealth of data show that, in hemodialysis patients, PhA positively correlates with nutritional status [48] and muscle function evaluated by HGS [49]. On the other hand, PhA also correlates positively with body cell mass and intracellular volume and negatively with the volume of extracellular fluid [41]. As a matter of fact, patients in cluster 2 showed extracellular fluid overload, a common characteristics of malnourished CKD patients, as indicated by higher ECW% and ECW/TBW values [50]. The lower PhA values in cluster 2 also suggest that patients belonging to this group have a lower body cell mass as compared with cluster 1 patients possibly because of the shift of water from the intracellular to the extracellular compartment or from a higher degree of tissue inflammation [51]. The difference in body composition parameters are consistent with the evidence that cluster 2 patients have a worse nutritional and muscle status as compared with those of cluster 1.

When considered the whole population, patients in cluster 1 had higher muscle mass and serum iron concentration than cluster 2 patients. We evaluated muscle mass by using BIA. Even though other diagnostic strategies can be used to this aim such as DEXA, CT scanning or NMR, ESPEN acknowledged BIA as a validated measurement for ASM estimation, though caution is recommended in patients with altered hydration [52,53]. Among the different algorithms that have been proposed to measure appendicular muscle mass using data from BIA we chose the Kyle

prediction equation [30] with further normalization to squared height since it is considered the predictive equation with the best performance to assess low muscle mass in non-dyalitic CKD patients, with the lowest mean difference (<1.5 kg) compared to DXA [54]. Even though ASMI is a reliable index of muscle mass, it cannot be used as the only parameter to distinguish between patients with initially impaired or preserved nutritional status because it may be biased, especially in CKD patients, by alteration in hydration and/or in the reciprocal distribution of water between the intra- and the extra-cellular compartments [55]. Some gender differences emerged from our cluster analysis. We observed, indeed, that serum iron concentration was higher in cluster 1 than in cluster 2 in males but not in females and ASMI in females but not in males. While the reason for gender difference in iron metabolism remain uncertain, we can speculate that the stronger effect on muscle mass of the partially impaired nutritional status in cluster 2, could be explained by the well-known differences in skeletal muscle fiber composition in males and females. Oxidative fibers, with a higher nutrient demand, are, indeed, more represented in females than in males, who, instead, show a higher percentage of glycolytic fibers [56].

In addition, no differences in serum albumin concentration were observed between cluster 1 and cluster 2 either in entire population than after gender stratification. This result may seem unexpected considering that serum albumin has been widely used as a marker of the nutritional status in several conditions including, for instance, older age [57] and, indeed, CKD [58]. However, the reliability of serum albumin has been seriously questioned on the basis of several considerations, such as the evidence that patients with hypoalbuminemia are not always malnourished and that nutrient supplementation does not necessarily increase serum albumin concentration proportionally [59].

Quite importantly, we found a significant difference between the two clusters of the entire population in energy intake which is a crucial determinant of nutritional status in CKD patients [60]. By contrast, the difference in energy intake was lost, after gender stratification, suggesting that this difference was actually due to the higher number of males in cluster 1 than in cluster 2. The evidence that, after stratifying patients by gender, the two clusters did not differ in calorie intake does not contradict our hypothesis that HGS and Hb concentration can be used to differentiate CKD patients with a worse nutritional status from those with a better nutritional status. In fact, other factors such as low-grade chronic inflammation, which is considered a hallmark of CKD, may induce malnutrition despite normal caloric intake.

Significantly, when cluster analysis was performed separately in males and females, HGS and Hb were still effective in dividing patients into two clusters. This excludes that the cluster separation observed in the whole population was due to the different representation of males and females in the two clusters. Remarkably, even after gender stratification, the two clusters separated by HGS and Hb were still different in the main indicators of nutritional status.

The present study has several strength and limitations. The major limitations are that the study was retrospective in design and that muscle mass was determined by using BIA. Because of the retrospective design of the study we do not have any definite indication that patients in cluster 2 would have actually progressed to PEW or that early nutritional or physical activity interventions would have halted this progression. Considering the use of BIA to assess muscle mass, the potential biases on the reliability of this technique in CKD could have altered our estimates of muscle mass. The main strength of the present study is that it was performed on a homogeneous patient population which was deeply investigated by the combined cooperation of highly trained nephrologists and nutritionists.

In conclusion, we showed that, despite gender differences, the combined use of two simple parameters as HGS and Hb blood concentrations, can discriminate between CKD patients who did not develop PEW yet but have a worse nutritional status and other CKD patients. Further prospective studies will be necessary to assess whether the early identification and treatment of these patients could help preventing PEW and improving CKD prognosis.

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Conflicts of interest

None to be disclosed.

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