Nutritional status evaluation and survival in haemodialysis patients in one centre from Romania

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Abstract

Background. Protein-energy wasting is a common complication and an important predictive factor for mortality in chronic dialysis patients. Therefore, nutritional status needs to be regularly assessed in these patients, by using several methods, and, if malnutrition is present, its possible causes should be thoroughly searched for and properly treated.

Material and Methods. In 149 prevalent haemodialysis patients (82 men, mean age 53.9 ± 13.7 years), we evaluated the nutritional status by anthropometrics [post-dialysis height (H), body weight (BW), body mass index (BMI), mid-arm circumference (MAC), tricipital skin-fold thickness (TST), mid-arm muscle circumference (MAMC), corrected mid-arm muscle area (cMAMA) and three-category subjective global assessment score (SGA)], biochemical tests [proteins equivalent of nitrogen appearance (nPNA), and pre-dialysis serum albumin, creatinine, total cholesterol, bicarbonate and haemoglobin (Hb) levels] and biochemical impedance analysis (BIA) to estimate body composition [percent body fat (%BF), fat-free mass (%FFM), body cell mass (%BCM), extracellular mass (%ECM) and the phase angle (PhA)].

Results. Age was found to be positively correlated with BMI ($P = 0.001$), and inversely correlated with %BCM ($P = 0.013$). Patients with A-category SGA were significantly younger (50.1 versus 63.7 years) than those with B-category SGA. Patients with diabetes had lower %BCM (32.9 versus 35.9; $P = 0.035$) and PhA (5.5 versus 6.9; $P = 0.0007$) than those without diabetes. The presence of heart failure was associated with significantly reduced nPNA (1.17 versus 1.34 g/kg day; $P = 0.014$), MAMC (22.0 versus 23.6 cm$^2$; $P = 0.041$), %BCM (33.0 versus 36.1; $P = 0.021$), PhA (5.8 versus 7.0; $P = 0.031$), serum albumin (39.7 versus 42.4 g/l; $P = 0.013$) and serum creatinine (8.1 versus 9.4 mg/dl; $P = 0.010$), and with a higher percent of B-category SGA (47.8% versus 22.6%; $P = 0.019$). Eleven deaths (7.4%) occurred during the follow-up period. Among general factors, age ≥ 55, the presence of diabetes, and dialysis vintage <2 years were associated with significantly reduced survival. Among nutritional factors, B-category SGA, nPNA < 1.2 g/kg day, %BF < 15% and PhA < 6° significantly predicted mortality in both Kaplan–Meier and Cox analyses. The most important risk factor appeared to be nPNA; for every 0.1 g/kg day increase in nPNA, death risk decreased by 15%.

Conclusions. In our haemodialysis patients, advancing age, diabetes and heart failure were associated with worse nutritional status, as estimated by anthropometry, biochemical markers and BIA. Age ≥55 years, the presence of diabetes, nPNA < 1.2 g/kg day, lower SGA score, %BF < 15% and PhA < 6° were associated with significantly increased death risk.

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Introduction

Protein-energy wasting (PEW) is a common and severe complication in patients with end-stage renal disease (ESRD). It involves multiple and complex aetiopathogenic mechanisms; insufficient food consumption, because of anorexia, on one hand, and metabolic disturbances induced by chronic uraemia and dialysis, on the other hand, are the main factors. Several large studies in ESRD patients, treated either by haemodialysis (HD) or by peritoneal dialysis (PD), have shown that a poor nutrient intake, as well as several clinical and biochemical markers of PEW are associated with increased morbidity and mortality [1–7]. However, it is often difficult to fully discriminate the relative influence of concurrent conditions: malnutrition, inflammation and comorbidities. Moreover, both inflammation and some comorbidities (such as congestive heart failure and chronic liver disease) have a strong impact on appetite and nutritional status.

Therefore, in patients with chronic kidney disease and ESRD, a regular evaluation of nutritional status is required during both pre-dialysis and dialysis stages, in order to detect PEW and its causes as early as possible, to treat and to prevent its worsening and its complications. In the past few years, United States [8] and European [9], as well as several national nephrology societies, have developed best practice guidelines indicating the strategy and the methods to evaluate the nutritional status in ESRD patients. These guidelines recommend the coordinated use of several methods (clinical, anthropometrical, biochemical and biophysical), seeing that there is no single ideal method to diagnose PEW. Recently, the International Society of Renal Nutrition and Metabolism (ISRNRM) proposed a definition of PEW in chronic and acute kidney disease [10]. According to this definition, PEW is diagnosed if three characteristics are present: low serum levels (of albumin, transthyretin or cholesterol), reduced body mass (low or reduced body or fat mass or weight loss with reduced intake of protein and energy) and reduced muscle mass (muscle wasting or sarcopenia, reduced mid-arm muscle circumference MAMC).

In Romania, the nutritional status in chronic dialysis patients has seldom been a subject of research until today. In this study, we aimed to evaluate the nutritional status, the risk factors for PEW, and the influence of PEW on survival in HD patients in a single large centre. For the first time in our country, we used bioelectrical impedance analysis (BIA) to measure the body composition in uraemic subjects.

Compared to dialysis populations in Western countries, dialysis patients in Romania are generally younger and with less severe comorbidities [11]. We believe these characteristics enabled us to evaluate the direct influence of nutritional status on survival, reducing the ‘background noise’ caused by concurrent risk factors and inflammation. We hypothesized that particularly in such dialysis patients the effect of malnutrition is unveiled even on short-term follow-up.

Materials and methods

Patients

For this study, we considered all prevalent HD patients in the Fresenius Nephrocare dialysis centre from Iaşi, Romania (n = 206). Of these, nine patients were excluded because of ongoing acute illnesses (infections, recent surgery, major cardiovascular events), 34 patients were excluded because of serum C-reactive protein (CRP) levels above 6.0 mg/l and 14 patients refused to participate. The remaining 149 patients (82 men) were included in the study, with their written informed consent.

Demographic data (age, gender and dialysis vintage), comorbidity conditions (diabetes mellitus; heart failure, defined as an echocardiographic ejection fraction below 40%) and the dialysis dose (h/week and eKt/V) were taken from the centre’s electronic data capture system (EUCLID 5). The patients’ mean follow-up was 13.5 ± 1.5 months (12 months at least).

Clinical and anthropometrical measurements

Body weight (BW) was measured at the end of an HD session (the ‘dry weight’). The body mass index (BMI) was calculated by the BW (kg) over height (H)² (m²) ratio. The tricipital skin-fold thickness (TST) was measured in the arm without arterio-venous fistula, at half distance between the acromion and the olecranon, using a Harpenden caliper, the result being given in centimetres (cm). The mid-arm circumference (MAC) was measured with a tape measure at the same level as the TST. The MAMC was calculated with the equation [12]

\[ \text{MAMC (cm)} = \text{MAC} - \pi \times \text{TST}. \]

The mid-arm muscle area (MAMA) was calculated with the equation

\[ \text{MAMA} = \text{MAMC}^2/4\pi. \]

The correction for gender of the MAMA (cMAMA) was done according to the equations [12]

In men: \( \text{cMAMA} = \text{MAMA} - 10 \)

In women: \( \text{cMAMA} = \text{MAMA} - 6.5. \)

Subjective global assessment (SGA) was based on history and physical examination, according to the method described by Detsky et al. [13], and the results were recorded on a special sheet. In the end, patients were classified in three categories (‘the SGA mark’) as follows: A (good nutrition), B (mild PEW) and C (severe PEW).

Biochemical measurements

We measured the pre-dialysis serum concentrations of blood urea nitrogen (BUN), serum creatinine, albumin, total cholesterol, haemoglobin (Hb) and bicarbonate.

The normalized equivalent of protein nitrogen appearance (nPNA) was calculated according to the equation [14]

\[ \text{nPNA (g/kg/day)} = 0.22 + \frac{0.036 \times \text{ID } \Delta \text{BUN} \times 24}{\text{ID interval (h)}}, \]

where ID ∆BUN is the increase in BUN between two consecutive dialysis sessions [interdialytic interval] = pre-dialysis BUN – post-dialysis BUN at the end of the previous HD session (mg/dl). In patients with residual urine output (> 100 ml/day), urinary nitrogen excretion was also taken into account; in this case, on the right-hand side of the equation we added the term [14]

\[ \frac{\text{Urinary urea nitrogen (g) \times 150}}{\text{ID interval (h)} \times \text{BW (kg)}} \]

Bioelectrical impedance analysis (BIA)

Both anthropometry and BIA measurements were performed within the first 30 min after the end of the HD session. By using the single-frequency (50 Hz) BIA-101AR, RJL Systems device, we directly measured the body resistance (R) and reactance (Xc). The results were processed with the Cyprus® software to determine the body composition, i.e. percent body fat (%BF), fat-free mass (%FFM), body cell mass (%BCM), extracellular mass (%ECM) and the phase angle (PhA).
Patients’ mean age was 53.9 ± 13.7 years. Diabetes was present in 15.1% and heart failure in 16.7% of cases. The biochemical measurements are presented in Table 1.

The anthropometrical mean values were as follows: BMI 22.8 ± 8.1 kg/m², MAC 26.7 ± 4.0 cm, TST 10.8 ± 6.4 mm, MAMC 23.3 ± 3.5 cm and cMAMA 35.7 ± 13.7 cm². The SGA was marked with an A in 73% and with a B in 27% of patients; there was no C mark in any patient. The mean values of BIA estimates were as follows: BF 23.4 ± 11.5%, FFM 76.6 ± 11.5%, BCM 35.4 ± 6.3%, ECM 41.2 ± 6.7% and PhA 6.73 ± 4.84°.

**Statistics**

To determine the significance and strength of associations, we used Pearson’s correlation coefficient $r$ for analyses of associations between continuous variables and Spearman rank for non-parametric variables. The $P$-values < 0.05 were considered as statistically significant. We used the Cox regression model and the Kaplan–Meier method for the survival analysis.

**Results**

The presence of heart failure was associated with significantly reduced survival. Death risk increased by 6.4% for every year of age. Among nutritional factors, B-category SGA, nPNA < 1.2 g/kg day, %BF < 15% and PhA < 6° significantly predicted mortality in both Kaplan–Meier and Cox analyses. The most important risk factor appeared to be nPNA. In the Cox model, for every 0.1 g/kg day increase in nPNA, death risk decreased by 15%, whereas in the Kaplan–Meier analysis, survival rate was 98.7% in patients with nPNA ≥ 1.2 versus 86.3% in those with nPNA < 1.2 ($P = 0.004$) (Table 2; Figure 1).

**Risk factors for PEW**

Age was found to be positively correlated with BMI ($r = 0.29, P = 0.001$), but inversely correlated with %BCM ($r = −0.20, P = 0.013$). Patients with A-category SGA were significantly younger (50.1 versus 63.7 years; $P < 0.0001$) than those with B-category SGA.

Diabetes and heart failure were comorbid conditions with a significant impact on nutrition. Patients with diabetes had a lower %BCM (32.9 versus 35.9%; $P = 0.035$) and PhA (5.5 versus 6.9°; $P = 0.0007$) than those without diabetes. The presence of heart failure was associated with significantly reduced nPNA (1.17 versus 1.34 g/kg day; $P = 0.014$), MAMC (22.0 versus 23.6 cm²; $P = 0.041$), PhA (5.8 versus 7.0°; $P = 0.031$), serum albumin (39.7 versus 42.4 g/l; $P = 0.013$) and serum creatinine (8.1 versus 9.4 mg/dl; $P = 0.010$), and with a higher percent of B-category SGA (47.8% versus 22.6%; $P = 0.019$).

**Survival analysis**

Eleven patients (7.4%) died during the follow-up period. Among general factors, age ≥ 55, the presence of diabetes and dialysis vintage < 2 years were associated with significantly reduced survival. Death risk increased by 6.4% for every year of age. Among nutritional factors, B-category SGA, nPNA < 1.2 g/kg day, %BF < 15% and PhA < 6° significantly predicted mortality in both Kaplan–Meier and Cox analyses. The most important risk factor appeared to be nPNA. In the Cox model, for every 0.1 g/kg day increase in nPNA, death risk decreased by 15%, whereas in the Kaplan–Meier analysis, survival rate was 98.7% in patients with nPNA ≥ 1.2 versus 86.3% in those with nPNA < 1.2 ($P = 0.004$) (Table 2; Figure 1).

**Discussions**

In this HD population, advancing age, diabetes and heart failure were associated with worse nutritional status, as estimated by anthropometry, biochemical markers and BIA. Age ≥ 55 years, the presence of diabetes, nPNA < 1.2 g/kg day, lower SGA score, %BF < 15% and PhA < 6° were associated with significantly increased death risk.

Our subjects were rather young and they had a relatively lower comorbidity burden, compared to a typical Western dialysis population. They received adequate dialysis, and the complications of uraemia, such as anaemia and metabolic acidosis were well controlled, according to the K/DOQI recommendations [8,16,17]. These premises may largely explain the overall good nutritional status, as well as the low mortality rate. We found that, in most patients, the clinical and biochemical nutritional markers were above the optimal levels recommended by the USA [8] and European [9] guidelines for HD patients. The prevalence of inflammation (CRP > 6 mg/l) was also lower (16.5%) than that reported in other HD cohorts, i.e. 30–50% according to a review by Arici and Walls [18]; the use of ultrapure water
dialysate in our centre may provide an explanation for this peculiarity.

The analysis of the correlations between demographic factors, dialysis dose and comorbid conditions, on one hand, and the nutritional markers, on the other hand, showed that age, diabetes and heart failure are predictive factors for PEW. Our findings are consistent with other studies. Advanced age is often associated with a higher rate of PEW because of typical difficulties in food gathering and cooking, poor appetite, frequent chronic or acute illnesses and reduced mobility and cognition [19]. Heart failure is commonly associated with a "malnutrition–inflammation–atherosclerosis" ("MIA") syndrome, through complex and still unclear mechanisms [20]; on the other hand, malnutrition may contribute to the alteration of myocardial systolic and diastolic functions [21]. Diabetes mellitus has also been previously identified as a risk factor for PEW in dialysis patients [22], being associated with accelerated muscle protein breakdown [23] and lean body mass loss [24].

The survival analysis showed that age ≥55, the presence of diabetes and the dialysis vintage <2 years were associated with a significantly higher death rate. If age and diabetes are well-known risk factors [25], the higher mortality rate seen in patients more recently started on HD in our centre might be explained by their older age (57 versus 53 years), their higher prevalence of heart failure (21% versus 16%) and their worse nutritional status as estimated by SGA and BIA, compared to those with a superior dialysis vintage.

Among the clinical and anthropometrical nutritional markers, the SGA emerged as the only predictive factor for survival. The SGA also correlated with %BF in men and with serum albumin. Therefore, we may consider SGA as a useful nutritional marker in HD patients. Besides, SGA has also been validated by others, who have shown its strong correlations with various nutritional markers [26] and its significant prognostic value for morbidity and mortality in ESRD patients [27]. Indeed, Enia et al. [26] found SGA to be correlated with MAMC, nPNA, serum albumin, %BF and PhA in 59 dialysis patients (36 HD, 23 PD), whereas Stenvinkel et al. [27], in a study of 206 ESRD patients, followed up for 3 years since starting on dialysis, have demonstrated SGA to be the only nutritional marker predicting survival in both males and females. Compared to our patients, those in Stenvinkel’s study had similar age (52 years), but greater diabetes prevalence (30%) and a high rate of cardiovascular disease (33%).

In our study the daily protein intake estimated by the nPNA was the most important predictive factor for survival: nPNA <1.2 g/kg day was associated with an 11-fold higher risk of death than nPNA ≥1.2 g/kg day. Indeed, nPNA has been a well-known risk factor for a long time. In the 1983 National Cooperative Dialysis Study (NCDS) nPNA >1 g/kg day was associated with reduced morbidity [28]. In 122 HD patients, Kalantar-Zadeh et al. also found nPNA as a predictive factor for hospitalization and mortality; independent of demographic factors, diabetic status and Kt/V [29]. The K/DOQI [8] and the European [30] guidelines for HD patients recommend nPNA to be at least 1.0 g/kg day. More recently, Kalantar-Zadeh et al. studied the relationship between nPNA and mortality in a U.S. cohort of almost 54 000 HD patients [31]. They noticed that a decrease in nPNA below 1.2 g/kg day during the first 6 months was followed by an increase in mortality in the following 18 months, whereas an increase in nPNA was associated with a reduction in death risk. In this study, the patients with nPNA between 1.0 and 1.4 g/kg day had the best survival rate and the mortality rate was significantly higher in both patients with nPNA <0.8 g/kg day and in those with nPNA >1.4 g/kg day. The authors speculated that increased mortality in patients with nPNA >1.4 g/kg day might be explained either by the toxicity of the high protein diet or by an underlying inflammatory hypercatabolic state.

Serum albumin—a very important predictive factor in many studies [1–6]—did not correlate with survival in our patients. Although serum albumin <40 g/l was associated with a >50% higher risk of death, this difference was not statistically significant, because of the insufficient power of our study. On the other hand, hypoalbuminaemia was found in a relatively small percentage of cases: 27.5% <40 g/l, 8% <35 g/l and only 1.3% (2 cases) <30 g/l.

The analysis of the influence of BIA-estimated body composition on survival showed that %BF <15% of body mass and PhA <6° were all significant risk factors for mortality. In HD patients, BIA may provide errors in the evaluation of body compartments, because in these patients there is often a higher degree of hydration of fat-free tissues [32]. No specific regression equations to determine FFM and BCM have been issued for uraemic patients, and the use of regression models derived from non-uraemic populations may lead to systematic errors [33]. Therefore, the K/DOQI guidelines do not recommend BIA as a valid method to estimate body composition in HD patients [8], although some authors have found significant correlations between BIA and reference methods like DEXA or NaBr [34]. The importance of BIA in dialysis patients seems to be mainly due to the observed correlation between PhA (actually, a measure of BCM) and survival, although it is unclear whether this correlation is indeed linked with the nutritional status. In a study including more than 3000 HD patients, followed up for 8 months on average, Chertow et al. [35], dividing the study population by PhA quintiles, found that those in the group with the lowest PhA had a 1.5 higher relative risk of mortality than those with the highest PhA, independent of age, gender, race, diabetes, serum albumin and serum creatinine. In 194 HD patients, Puppin et al. [36] showed that PhA is an independent predictive factor of general and cardiovascular mortality. In PD patients, Avram et al. [37,38] found a PhA ≥6° to be associated with significantly better survival than PhA <6°. Our study confirmed the predictive value of PhA in HD patients and also demonstrated—for the first time, as far as we know—the influence of BIA-estimated %BF and %BCM on survival in these patients. Previously, the predictive value of %BF on survival was shown by Kalantar-Zadeh et al. by using near-infrared interactance [39].

Finally, it is to say that our study also had several limitations: (1) the inclusion of prevalent and not incident HD patients (which would have eliminated the influence of dialysis vintage); (2) the relatively short duration of follow-up (whereas a longer duration might have revealed more significant mortality risk factors); and (3) the absence of a more
References


Conflict of interest statement. Prof. Dr. A. Covic is a scientific consultant for Fresenius Medical Care and a member of the speakers’ bureau of Roche and of the advisory boards of Affymax and Vifor. The other authors have no conflicts of interests to declare.