Creatinine index and transthyretin as additive predictors of mortality in haemodialysis patients

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Abstract

Background. Malnutrition and inflammation are recognized as important predictors of poor clinical outcome in haemodialysis (HD). This study was designed to estimate the relative contribution of known biological markers of inflammation, malnutrition and muscle mass in the prognosis of HD patients.

Methods. A total of 187 HD patients (100 women, 87 men, median age 66.7 years [22.3–93.5]) were followed-up yearly for 5 years. At baseline, pre-dialysis values of C-reactive protein (CRP), albumin, transthyretin, total HDL- and LDL-cholesterol and triacylglycerol were determined. Estimation of creatinine index (CI) as muscle mass marker was determined by creatinine kinetic modelling using pre- and post-dialysis creatinine values.

Results. During the follow-up period, 89 deaths (53 from cardiovascular causes) were observed. After adjustment for age, gender, dialysis vintage, smoking, diabetes mellitus and hypertension, the highest tertile of CRP and lowest tertile of transthyretin and CI were significantly associated with all-cause mortality (relative risk (RR) = 1.98 [1.12–3.47], 2.58 [1.48–4.50], 2.71 [1.42–5.19], respectively). In addition, low CI had an additive value to low levels of transthyretin. In contrast, high cholesterol (RR = 0.47 [0.27–0.83], P = 0.0091) and vitamin E concentrations (RR = 0.46 [0.26–0.80], P = 0.006) showed a protective trend for all-cause mortality. In the multivariate analysis, transthyretin appeared as the most predictive biological marker of non-CV mortality (RR = 3.78 [1.30–10.96], P = 0.014), and CI of CV mortality (RR = 2.61 [1.06–6.46], P = 0.038), respectively.

Discussion. These results confirm that uraemic malnutrition constitutes an important risk factor for mortality in HD. Beyond transthyretin, CI seems to be an additional marker routinely available and monthly determined in HD patients.

Keywords: creatinine index; haemodialysis; malnutrition; mortality; transthyretin

Introduction

In spite of a clear improvement in dialysis technologies during the last years, the death rate among uraemic patients treated by haemodialysis (HD) has always been rather high compared to the general population. It is mostly due to cardiovascular (CV) diseases [1,2]. Nutritional status has long been recognized as an important predictor of poor clinical outcome in these patients [3,4]. Malnutrition in uraemia appears as a multifactorial process [5] mainly due to energetic metabolism impairment, enhancement of catabolic rate and finally inflammation [2]. Chronic kidney disease patients also spontaneously restrict their dietary protein intake, while uraemia by itself is a net catabolic status [6]. Moreover, the HD procedure affects the whole body and muscle protein homeostasis [7], inducing protein catabolic effects such as an alteration of amino acid transport kinetics and an increase of protein turnover [8].

During the last decade, C-reactive protein (CRP) has emerged as an important determinant of both clinical outcome and nutritional status [2,9]. The deleterious association of inflammation and malnutrition firstly
highlighted in atherogenesis [10] has been further extended to other long term HD complications. The concept of malnutrition inflammation complex syndrome (MICS) defined by Kalantar-Zadeh et al. [2] suggests that beyond inflammation, amplification loops involving malnutrition could drive numerous features of uraemia.

Muscle metabolism alteration should be considered as the consequence of the uraemic protein-energetic disorders aggravated by inflammation. In fact, it has been shown that muscle amino acid transport alterations could be prevented by increasing amino acid delivery via extracorporeal circuit. Similarly, pre-dialytic nutritional support could partially prevent HD-related malnutrition including muscle-mass catabolism [11]. In addition, chronic inflammatory state results in an enhancement of muscle catabolism and release of amino acids [8,12]. The HEMO study has recently stressed the importance of muscle mass as determined by anthropometric data in clinical outcome [13]. However, exploring muscle metabolism requires specialized methods involving radioisotopes [7]. Alternatively, it has been shown that creatinine modelling could be a simple non-invasive and clinically relevant method to assess muscle mass [14]. In a previous work [15], we reported a clear association between the prevalence of CV disease and end-stage renal disease (ESRD)-associated metabolism disorders such as inflammation and undernutrition, using creatinine-derived estimations of lean body mass (LBM) and other markers such as transthyretin. The present study was designed to assess the prognostic value of these markers on CV and non-CV mortality.

Subjects and methods

Study design

One hundred and ninety-two stable HD patients recruited in one of the three dialysis facilities of Montpellier (France) [a hospital-based facility (Lapeyronie University Hospital), a public non-profit association (AIDER) and a private dialysis clinic (CHLM)] were evaluated for inclusion from October to November 2001. Informed consent was obtained from all participants.

Patients received either standard HD (n = 166) or haemodiafiltration (HDF) treatments with online ultra-pure bicarbonate-based dialysate (n = 26). All patients were dialysed with low (n = 109) or high-flux (n = 83) polysulphone membranes. Patients with symptoms or signs of acute inflammatory or infectious diseases were excluded from the study.

The included patients were then prospectively followed-up yearly until 5 January 2007.

Baseline data

Medical charts were reviewed for age, gender, weight, height, underlying renal disease, dialysis vintage, history of transplantation, diabetes mellitus, current hypertension, comorbid conditions, past or current smoking and current medication. Existence of hypertension was defined by pre-dialysis blood pressure higher or equal to 140/90 mmHg and/or by a current anti-hypertensive treatment. The efficiency of dialysis was estimated by calculation of Kt/V (K, clearance of urea of the dialyser, t, time of dialysis and V, volume of purified urea) [16].

Laboratory analysis and procedures

Pre- and post-dialysis blood samples were collected before and after a mid-week dialysis session according to the best practices applied for dialysis adequacy evaluation [16]. Blood samples were centrifuged, treated, analysed for routine parameters and finally stored at –80°C, in order to perform additional analyses.

Evaluation of routine parameters was carried out on an automate Olympus AU2700 (Rungis, France). It used an immunoturbidimetric technique for determination of albumin, transthyretin and high-sensitive CRP concentrations, and an immunoenzymatic technique for determination of urea and creatinine. Plasma concentrations of total cholesterol (TC), HDL-cholesterol (HDL) and triacylglycerols (TG) were measured by an enzymatic technique (KonePro, Konelab). The LDL-cholesterol (LDL) rate was calculated by the Friedwald’s formula: [LDL = TC – (TG/5) – HDL]. Plasma vitamin E concentration was determined by HPLC method as previously described [17]. Results were normalized and expressed as VitE/(chol + TG) (μmol/mmol ratio).

Measurement of nutritional indices

Body mass index (BMI) was obtained from height and post-dialysis body weight according to the formula BMI = Weight (kg)/Height (m2). The creatinine index (CI) was computed from creatinine kinetic modelling as described previously. Briefly, CI was deduced from creatinine generation rate using a single-pool variable volume model [14,18] according to the following formula:

CI(mg/kg/day) = 162.7 × GCr/BWpost + 0.00429 × TACr,lmm

where GCr = Creatinine generation rate, BWpost =post-dialysis weight, TACr,lmm = logarithmic mean-based, time-averaged creatinine concentration.

Follow-up period and end point

Patients were followed yearly for 5 years. They were not significantly modified in terms of dialysis treatment and schedules during this follow-up period. Each year, for 5 years, all subjects were re-evaluated by the physicians in the dialysis centres.

The dates of death, transplantation or transfer to another dialysis centre were documented. The causes of death were classified as follows:

- Cardiovascular events (myocardial infarction, congestive heart failure and sudden death)
- Non-CV events (infection, neoplasm, other and unknown causes).
**Statistical analysis**

Descriptive statistics are presented as percentages for categorical variables, as means with SEM for normally distributed variables and as medians with ranges for non-normally distributed variables.

The Kaplan–Meier method was used to describe survival curves. The Cox proportional hazards model was used to identify predictors of mortality. In this manner, deaths were analysed in the three following groups: all-causes, CV and non-CV mortality. Continuous variables were divided into tertiles. Association of deaths with non-traditional risk factors was estimated with relative risks (RR) and their 95% confidence intervals (95% CI) adjusted for age, gender, dialysis vintage, diabetes mellitus, smoking and hypertension. According to the literature, these last three factors are traditional risks factors for mortality in HD patients.

Significance was set at $P < 0.05$. Five patients (2.6%) had some missing data (five values of HDL cholesterol because of triacylglycerol values higher than 5 g/l), leaving 187 patients for the statistical analysis.

Statistical analyses were performed using the SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

**Results**

**Patient characteristics and outcome**

One hundred and eighty seven patients (87 males and 100 females) were included in the statistical analysis of this prospective study. Median age of this population was 66.7 years [22.3–93.5]. The median time spent on dialysis was 4.82 years [0.06–30.28], and their median time spent on dialysis was 66.7 years [22.3–93.5]. The median time spent on dialysis was 66.7 years [22.3–93.5].

**Univariate analysis**

Conventional markers of nutrition and inflammation. As reported in Table 1, by comparison with the first tertile of CRP ($<4.21$ mg/l), the highest tertile ($\geq 12.58$ mg/l) was significantly associated with all-cause (RR = 1.98 [1.12–3.47], $P = 0.0182$) and non-CV mortality (RR = 2.69 [1.13–6.40], $P = 0.0254$), while the tendency observed with CV mortality did not reach significance (RR = 1.51 [0.71–3.19]).

Among all plasma nutritional parameters observed, transthyretin was the most predictive marker of mortality with regard to all-cause and non-CV deaths (for the lowest tertile: RR = 2.58 [1.48–4.50], $P = 0.0008$; RR = 5.72 [2.17–15.08], $P = 0.0004$, respectively). In contrast, the association between low levels of transthyretin and CV mortality did not reach significance (RR = 1.64 [0.81–3.31]). Kaplan–Meier analysis accordingly to tertiles of transthyretin is showed in Figure 1.

Finally, neither BMI nor serum albumin were predictive factors of mortality.

Lipid parameters as outcome predictors. Comparing with the first tertile, high total and LDL cholesterol concentrations were significantly associated with reduced all-cause mortality (RR = 0.47 [0.27–0.83], $P = 0.0091$; RR = 0.37 [0.20–0.66], $P = 0.0008$, respectively). Surprisingly, LDL cholesterol was similarly associated with a significant reduction of CV and non-CV mortality. Low concentrations of HDL cholesterol were significantly associated with increased all-cause and CV mortality (RR = 1.71 [1.00–2.94], $P = 0.0493$ and RR = 2.07 [1.01–4.22], $P = 0.0466$, respectively).

Crude vitamin E concentration appeared as a protective factor for all-cause and non-CV mortality (RR = 0.46 [0.26–0.80] $P = 0.0060$, and RR = 0.27 [0.11–0.66], $P = 0.0042$ respectively for the highest tertile). However, when vitamin E levels were standardized for cholesterol and triglyceride levels, this relationship was totally abolished.

Muscle mass estimated from creatinine kinetic modelling. After adjustment for traditional risk factors (age, gender, dialysis vintage, diabetes, smoking and hypertension), a significant association between low levels of pre-dialytic creatinine and all-cause and CV mortality (RR = 2.33 [1.28–4.24], $P = 0.0057$ and RR = 2.30 [1.0864.89], $P = 0.0301$, respectively) was observed, while none was observed with non-CV mortality. This association was further observed and enhanced for CI derived from pre- and post-creatinine values. Indeed, low values of CI were significantly associated with all-causes, CV and non-CV mortality (RR = 2.71 [1.42–5.19], $P = 0.0026$; RR = 2.63 [1.14–6.08], $P = 0.0231$; RR = 2.94 [1.04–8.34], $P = 0.0420$ respectively). Kaplan–Meier curve according to tertiles of CI is showed in Figure 2.

Finally, since CI appears as a predictive marker assessing somatic protein metabolism and malnutrition inflammation complex syndrome severity, we explored the potential additive association between CI and transthyretin. As shown in Figure 3, transthyretin and CI are clearly additives in predicting poor outcome in HD patients in all-cause as well as in CV mortality.

**Multivariate analysis**

Table 2 describes the proportional hazards model using all of the parameters that were significantly associated with mortality in the previous analysis, which includes CRP, transthyretin, CI (which is more predictive than pre-dialysis creatinine in univariate analysis),
total cholesterol (rather than LDL cholesterol which was calculated from total and HDL cholesterol). In addition, classical risk factors such as age, gender, dialysis vintage, smoking, diabetes mellitus and hypertension were included.

Age was significantly associated with overall mortality, while the tendency observed with other traditional risk factors such as diabetes mellitus, hypertension, gender and smoking did not reach significance. Similarly, age and smoking were associated with CV mortality. With respect to non-traditional risk factors, CRP did not appear as a predictor of mortality when all factors were taken into account. The association of low concentrations of transthyretin with all-cause mortality and especially with non-CV mortality remained highly significant (RR = 1.89 [1.02–3.50], \( P = 0.0434 \); RR = 3.78 [1.30–10.96], \( P = 0.0145 \), respectively). In contrast, CI was significantly associated with all-cause and CV mortality (RR = 2.19 [1.10–4.35], \( P = 0.0251 \); RR = 2.61

Table 1. Cox proportional-hazards analysis of factors predicting all-cause mortality (\( n = 89 \)), cardiovascular mortality (\( n = 53 \)) and non-cardiovascular mortality (\( n = 36 \)) among haemodialysis patients adjusted for age, gender, dialysis vintage, diabetes, smoking and hypertension

|                      | All causes |                                      | Cardiovascular causes |                                      | Non-cardiovascular causes |                                      |
|----------------------|------------|---------------------------------------|-----------------------|---------------------------------------|---------------------------|---------------------------------------|
|                      | RR [CI 95%] | \( P \)                               | RR [CI 95%]           | \( P \)                               | RR [CI 95%]               | \( P \)                               |
| CRP (mg/l)           |            |                                       |                       |                                       |                           |                                       |
| <4.21                | 1          |                                       | 1                     |                                       |                           |                                       |
| [4.21–12.58]         | 1.22       | 0.67–2.20 NS                           | 0.94                  | 0.43–2.06 NS                          | 1.65                      | 0.67–4.09 NS                          |
| \( \geq 12.58 \)     | 1.98       | 1.12–3.47 0.0182                      | 1.51                  | 0.71–3.19 NS                          | 2.69                      | 1.13–6.40 0.0254                      |
| Transhcyptin (g/l)   |            |                                       |                       |                                       |                           |                                       |
| <0.25                | 2.58       | 1.48–4.50 0.0008                      | 1.64                  | 0.81–3.31 NS                          | 5.72                      | 2.17–15.08 0.0004                     |
| [0.25–0.31]          | 1.66       | 0.97–2.85 0.0656                      | 1.30                  | 0.67–2.52 NS                          | 2.71                      | 1.02–7.16 0.0447                      |
| \( \geq 0.31 \)      | 1          |                                       | 1                     |                                       |                           |                                       |
| Albumin (g/l)        |            |                                       |                       |                                       |                           |                                       |
| <35.48               | 0.90       | 0.53–1.54 NS                           | 0.85                  | 0.42–1.71 NS                          | 1.00                      | 0.43–2.29 NS                          |
| [35.48–39.06]        | 0.88       | 0.52–1.51 NS                           | 0.95                  | 0.47–1.89 NS                          | 0.80                      | 0.34–1.87 NS                          |
| \( \geq 39.06 \)     | 1          |                                       | 1                     |                                       |                           |                                       |
| BMI (Kg/m²)          |            |                                       |                       |                                       |                           |                                       |
| <21.24               | 1.24       | 0.71–2.14 NS                           | 1.34                  | 0.66–2.76 NS                          | 1.10                      | 0.46–2.59 NS                          |
| [21.24–25.27]        | 1.11       | 0.65–1.90 NS                           | 1.10                  | 0.54–2.21 NS                          | 1.13                      | 0.48–2.64 NS                          |
| Total cholesterol (mmol/l) |        |                                       |                       |                                       |                           |                                       |
| <4.37                | 0.96       | 0.59–1.59 NS                           | 1.15                  | 0.60–2.22 NS                          | 0.75                      | 0.34–1.62 NS                          |
| [4.37–5.52]          | 0.47       | 0.27–0.83 0.0091                      | 0.58                  | 0.28–1.22 NS                          | 0.34                      | 0.14–0.83 0.0173                     |
| Triglycerides (mmol/l) |            |                                       |                       |                                       |                           |                                       |
| <1.34                | 0.59       | 0.34–1.01 NS                           | 0.72                  | 0.34–1.54 NS                          | 0.44                      | 0.20–0.98 0.0453                     |
| [1.34–2.28]          | 0.85       | 0.51–1.42 NS                           | 1.49                  | 0.76–2.94 NS                          | 0.35                      | 0.15–0.84 0.0187                     |
| HDL cholesterol (mmol/l) |       |                                       |                       |                                       |                           |                                       |
| <0.94                | 1.71       | 1.00–2.94 0.0493                      | 2.07                  | 1.01–4.22 0.0466                      | 1.33                      | 0.57–3.09 NS                          |
| [0.94–1.15]          | 1.30       | 0.76–2.23 NS                           | 1.32                  | 0.63–2.75 NS                          | 1.29                      | 0.58–2.87 NS                          |
| \( \geq 1.15 \)      | 1          |                                       | 1                     |                                       |                           |                                       |
| LDL cholesterol (mmol/l) |         |                                       |                       |                                       |                           |                                       |
| <2.42                | 0.76       | 0.46–1.25 NS                           | 0.72                  | 0.38–1.38 NS                          | 0.82                      | 0.38–1.80 NS                          |
| [2.42–3.34]          | 0.37       | 0.20–0.66 0.0008                      | 0.37                  | 0.17–0.80 0.0012                      | 0.36                      | 0.14–0.88 0.0248                     |
| \( \geq 3.34 \)      | 1          |                                       | 1                     |                                       |                           |                                       |
| Vitamin E (μmol/l)   |            |                                       |                       |                                       |                           |                                       |
| <26.2                | 0.51       | 0.31–0.85 0.0099                      | 0.66                  | 0.34–1.29 NS                          | 0.35                      | 0.16–0.80 0.0122                     |
| [26.2–34.4]          | 0.46       | 0.26–0.80 0.0060                      | 0.66                  | 0.32–1.36 NS                          | 0.27                      | 0.11–0.66 0.0042                     |
| \( \geq 34.4 \)      | 1          |                                       | 1                     |                                       |                           |                                       |
| Adjusted Vitamin E (μmol/mmol) |     |                                       |                       |                                       |                           |                                       |
| <4.13                | 1.20       | 0.72–2.00 NS                           | 1.01                  | 0.51–1.99 NS                          | 1.46                      | 0.67–3.19 NS                          |
| [4.13–4.77]          | 0.88       | 0.52–1.50 NS                           | 0.80                  | 0.41–1.59 NS                          | 0.95                      | 0.40–2.25 NS                          |
| Pre-dialytic creatinine (μmol/l) |     |                                       |                       |                                       |                           |                                       |
| <692                 | 2.33       | 1.28–4.24 0.0057                      | 2.30                  | 1.08–4.89 0.0301                      | 2.46                      | 0.90–6.70 0.0783                     |
| [692–852]            | 1.61       | 0.87–2.99 NS                           | 1.44                  | 0.65–3.21 NS                          | 1.90                      | 0.70–5.18 NS                          |
| \( \geq 852 \)       | 1          |                                       | 1                     |                                       |                           |                                       |
| Creatinine index (mg/kg/j) |       |                                       |                       |                                       |                           |                                       |
| <15.2                | 2.71       | 1.42–5.19 0.0026                      | 2.63                  | 1.14–6.08 0.0231                      | 2.94                      | 1.04–8.34 0.0420                     |
| [15.2–18.9]          | 2.05       | 1.08–3.89 0.0292                      | 2.27                  | 0.99–5.23 0.0541                      | 1.87                      | 0.67–5.22 NS                          |
| \( \geq 18.9 \)      | 1          |                                       | 1                     |                                       |                           |                                       |
[1.06–6.46, \( P = 0.0380 \), respectively] but not with non-CV mortality.

**Discussion**

This prospective study confirms the high annual mortality rate (9.5%) observed in the HD population [1]. Our results confirm previous observations showing that transthyretin is an independent determinant of mortality in HD patients. In addition, we showed in this study that muscle-mass determination by CI derived from creatinine modelling has an additive value to transthyretin in all-cause and CV mortality.

Assessment of protein and energy nutritional status can be achieved by determination of visceral and somatic proteins, in addition to measurement of energy balance [19]. Visceral protein stores can be determined easily by measurement of biochemical circulating markers such as serum albumin or transthyretin. Usually, studies define serum albumin as the most reliable indicator of nutritional status [20] despite limitations due to the cytokine-induced increase in fractional synthesis rate [19] potentially hiding hypoalbuminaemia. On the other hand, hypoalbuminaemia could be due to non-nutritional causes such as increased losses through gastrointestinal tract or volume perturbations. Previous studies have underlined that transthyretin, a negative acute phase protein known as a complex transporter of thyroxine, retinol-binding protein and vitamin A, showed higher correlation coefficients with nutritional indices than albumin and appeared to be better and quickly reflects nutritional status changes [21]. Indeed, transthyretin levels, but not albumin levels were correlated with arm muscle circumference, triceps skin fold [21,22] or LBM [23]. Recently, Chertow et al. [24] have reported that transthyretin levels were directly related to nutritional parameters and dietary intake such as body weight, pre-dialysis blood urea nitrogen, creatinine, albumin, phosphorus and bicarbonate. In addition, transthyretin levels, but not albumin, are predictive of CV hospitalization. According to these data, monthly transthyretin measurement is recommended by both the American and European consensus group in the nutritional assessment of dialysis patients [25,26].

![Fig. 1. Survival curve of haemodialysis patients according to transthyretin tertiles; all-cause deaths.](image1)

![Fig. 2. Survival curve of haemodialysis patients according to creatinine index tertiles; all-cause deaths.](image2)

![Fig. 3. Creatinine index and transthyretin: additive predictive markers of all-cause (A) and cardiovascular (B) mortality. Patients were divided into six groups according to transthyretin (considered as tertiles) and creatinine index values. Number of patients was as follows: low creatinine index (<15.2), \( n = 24, 26 \) and 12 for low, median and high transthyretin values, respectively. High creatinine index (≥15.2), \( n = 32, 32 \) and 61 for low, median and high transthyretin values, respectively.](image3)
In the present study, both univariate and multivariate analyses underline transthyretin as a more powerful predictor of all-cause mortality in the HD population compared to albumin. In fact, in this long-term follow-up study, the lowest tertile value of albumin did not appear as a significant predictor of mortality. This result, in apparent contradiction with the K/DOQI guidelines or DOPPS observational study [28,29], could be due to the relatively low size of our population. On the other hand, it should be underlined that in our population the lowest tertile value was 35.48 g/l, a threshold value that is above risk. In comparison, the median value observed for albumin in the HEMO study was 36.3 g/l and the lowest values of albumin, corresponding to a clearly enhanced mortality risk, were 26–32 g/l [13]. Low albumin levels are rarely observed in our population (only 27 patients had albumin levels lower than 32 g/l).

In addition, in the same study, it was shown that low albumin was a predictive indicator on short term but that the predictive RR diminished with extending follow up period (>6 months). Taken together, these data suggest that in our population with a high dialysis dose (averaged \( \frac{Kt}{V} \) of 1.47/0.02), with less than one-third of the patients lower than the nutrition K/DOQI recommendations, transthyretin appears as a better long-term predictor of mortality than albumin. The significant involvement of transthyretin in long-term poor outcome of HD patients is confirmed with the multivariate analysis (Table 2). Transthyretin is a powerful indicator of all-cause (RR = 1.89 [1.02–3.50], \( P = 0.0434 \)) and non-CV (RR = 3.78, [1.30–10.96] \( P = 0.0145 \)) mortality, but not of CV mortality in agreement with a previous study [24] reporting predictive value on infection-related mortality. This long-term predictive value could be due in part to the reduced transthyretin turnover resulting in an increase in half-life in ESRD or to the binding into a macromolecular complex with an extra-vascular diffusion lower than albumin [21].

While serum markers reflect visceral proteins, somatic proteins are a determinant of muscle mass [4]. Therefore, the assessment of somatic protein status appears of crucial clinical relevance and is commonly used for assessment of nutritional status in ESRD patients [19]. Several techniques are used to determine LBM, such as anthropometric measurements, DEXA (dual energy X-ray absorptiometry) or isotopic determination with \([^{1}H\)-leucine [7], which are expensive and difficult to implement in clinical practice.

In contrast, creatinine kinetic, which is based on the principle that creatinine production is proportional to LBM and represents the sum of creatinine excretion (urinary and dialytic) and metabolic degradation, is a simple and a reliable tool for the assessment of protein nutritional status and muscle mass in HD patients.

| Table 2. Final multivariate cox proportional-hazards analysis of factors predicting all-cause, cardiovascular and non-cardiovascular mortality among haemodialysis patients adjusted for age, gender, dialysis vintage, diabetes, smoking and hypertension |
|---|---|---|---|
| All causes | Cardiovascular | Non-cardiovascular |
| | RR | [CI 95%] | \( P \) | RR | [CI 95%] | \( P \) | RR | [CI 95%] | \( P \) |
| Transthyretin (g/l) | | | | | | | | | |
| <0.25 | 1.89 | 1.02–3.50 | 0.0434 | 1.34 | 0.60–2.96 | NS | 3.78 | 1.30–10.96 | 0.0145 |
| [0.25–0.31] | 1.25 | 0.67–2.33 | NS | 1.07 | 0.49–2.35 | NS | 1.93 | 0.66–5.61 | NS |
| \( \geq 0.31 \) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Creatinine index (mg/kg/j) | | | | | | | | | |
| \(< 15.2 \) | 2.19 | 1.10–4.35 | 0.0251 | 2.61 | 1.06–6.46 | 0.0380 | 1.80 | 0.63–5.20 | NS |
| \([ 15.2–18.9 \) | 1.67 | 0.87–3.21 | NS | 2.21 | 0.93–5.23 | 0.0723 | 1.26 | 0.45–3.54 | NS |
| \( \geq 18.9 \) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Total cholesterol (mmol/l) | | | | | | | | | |
| \(< 4.37 \) | 1.24 | 0.71–2.15 | NS | 1.56 | 0.73–3.33 | NS | 0.91 | 0.40–2.07 | NS |
| \([ 4.37–5.52 \) | 0.69 | 0.37–1.26 | NS | 0.82 | 0.36–1.84 | NS | 0.56 | 0.22–1.44 | NS |
| \( \geq 5.52 \) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| CRP (mg/l) | | | | | | | | | |
| \(< 4.21 \) | 0.89 | 0.47–1.68 | NS | 0.70 | 0.30–1.64 | NS | 1.08 | 0.40–2.87 | NS |
| \([ 4.21–12.58 \) | 1.42 | 0.78–2.59 | NS | 1.26 | 0.57–2.76 | NS | 1.45 | 0.57–3.71 | NS |
| \( \geq 12.58 \) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Gender | | | | | | | | | |
| Men | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Women | 0.98 | 0.58–1.66 | NS | 0.68 | 0.33–1.40 | NS | 1.54 | 0.68–3.50 | NS |
| Age for 1 SD increase | 1.93 | 1.39–2.71 | <0.0001 | 2.40 | 1.53–3.82 | 0.0002 | 1.42 | 0.88–2.30 | NS |
| Dialysis vintage for 1 SD increase | 1.06 | 0.80–1.41 | NS | 1.24 | 0.84–1.84 | NS | 0.86 | 0.57–1.31 | NS |
| Hypertension | | | | | | | | | |
| No | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Yes | 1.68 | 0.92–3.07 | 0.0905 | 1.46 | 0.64–3.34 | NS | 1.99 | 0.82–4.85 | NS |
| Diabetes | | | | | | | | | |
| No | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Yes | 1.45 | 0.86–2.45 | NS | 1.70 | 0.86–3.36 | NS | 1.18 | 0.50–2.79 | NS |
| Smoking | | | | | | | | | |
| No | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Yes | 1.71 | 0.99–2.94 | 0.0550 | 2.52 | 1.28–4.97 | 0.0076 | 0.81 | 0.30–2.22 | NS |
patients that can be easily coupled to urea kinetics modelling [18,30,31]. Such indices derived from creatinine kinetic (CI, observed LBM, observed/expected LBM) have been identified as prognostic markers of mortality in HD patients [14,32], but none of these studies could establish the link between creatinine metabolism and CV risk. Our study adjusted for traditional risk factors established a clear relationship between CI and all-cause, CV and non-CV mortality. This observation is in agreement with the previous observation of the HEMO study [13] showing that low pre-dialysis creatinine value is an index of poor prognosis. Indeed, CI is directly linked to creatinine production, thus to muscle mass, and is not influenced by dialysis efficacy. The multivariate analysis confirmed the powerful relationship of CI among biological somatic protein markers with HD mortality, particularly when the cause of death was CV disease (RR = 2.61, [1.06–6.46], P = 0.038, after full adjustment). Our results highlight two interesting facts. Firstly, the predictive value of both CI and transthyretin are maintained over time from 2 to 5 years of follow-up (Figure 4). Second, multivariate analysis shows that CI and transthyretin are independent, and therefore additive risk factors for all-cause and also for CV mortality (Figure 3). Sarcopenia in stable HD patients is another expression of the malnutrition inflammation complex syndrome that should be detected early in HD patients, since it is associated with a high mortality risk. The close association between inflammation and malnutrition [10,12] has been highlighted during the past decade. It has also been suggested that inflammation is an underlying component of ‘reverse epidemiology’ [2,33]. This term indicates that certain classical risk markers (such as dyslipidaemia, high BMI or hypertension) become protective factors for CV morbidity in the HD population. Analysis of lipid parameters confirms the paradoxical association between high concentrations of total and LDL-cholesterol and decreased mortality of HD patients (RR = 0.47 [0.27–0.83], P = 0.0091; RR = 0.37 [0.30–0.66], P = 0.0008, respectively for all-causes death, fully adjusted). Interestingly, it appears that lipid levels drive also the relationship between vitamin E and mortality. Indeed, the protective effect of crude level of vitamin E was totally abolished after normalization by cholesterol and triglyceride levels. In this long-term follow-up study, CRP levels adjusted for age, gender, dialysis vintage, diabetes, smoking and hypertension appear as a predictive risk factor for overall and non-CV mortality but not for CV disease (RR (1.51 [0.71–3.19], NS) in univariate analysis. It has been shown that CRP levels are dependent on several individual factors including age, gender, hypertension, glucose metabolism and smoking taken as adjustment factors in the statistical analysis [34]. If we consider the crude CRP levels without any adjustment, the RR for CV mortality reaches significance (RR = 2.05 [1.06–3.974], P = 0.0327) in agreement with previous studies [2,5,9,10,15]. The key role of inflammation in haemodialysis-induced malnutrition was further supported by the relationship between CRP and transthyretin (P < 0.0001), CI (P = 0.019), total cholesterol (P = 0.006) and vitamin E (P = 0.0628). In addition, it has been recently reported that the increased mortality associated with low cholesterol level is only observed in inflammatory HD patients [35]. In conclusion, in the present study, mortality in HD patients was associated with traditional risk factors such as age, smoking and hypertension, whereas an opposite relation was observed with dyslipidaemia. Uraemic malnutrition, as reflected by visceral and somatic protein status markers, constituted the most important risk factor for poor clinical outcomes in these patients. In practical terms, levels of

![Fig. 4. Creatinine index and transthyretin as predictive markers of mortality: trends in relative risks over time.](https://academic.oup.com/ndt/article-abstract/23/1/345/1925472/Downloaded-from-https://academic.oup.com/ndt/article-abstract/23/1/345/1925472)
transhyretin, as a reliable index of visceral protein, and CI, as a marker of muscle mass, were independent predictors of poor outcome in HD patients with additive effect. In order to determine appropriate diet protein supplementation and to reduce inflammation-related mortality, we propose the monthly assessment of transhyretin and CI as a simple and convenient technique for the routine nutritional assessment of HD patients. This biological index could improve assessment of MICS severity, in addition to clinical scores such as SGA (Subjective Global Assessment) or a composite index such as MIS (malnutrition inflammation score) [36] taking into account only visceral proteins.

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Conflict of interest statement
None declared.

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