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Abstract

Background: Malnutrition and inflammation are recognized as important predictors of poor clinical outcome in hemodialysis (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: 187 HD patients (100 women, 87 men, median age : 66.7 years [22.3-93.5]) were followed-up yearly for five 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 (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. By 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 uremic malnutrition constitutes an important risk factor for mortality in HD. Beyond transthyretin, creatinine index seems to be an additional marker routinely available and monthly determined in HD patients.

Keywords: creatinine index, malnutrition, mortality, transthyretin, hemodialysis

Running title : Nutritional indices of mortality in HD

Introduction

In spite of a clear improvement in dialysis technologies during the last years, the death rate among uremic patients treated by hemodialysis (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, 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 Syndrom (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 uremic proteino-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 extracorporal circuit. Similarly, perdialytic nutritional support could partially prevent HD related malnutrition including muscle mass catabolism [11]. In addition, chronic inflammation state results in an enhancement of muscle catabolism and release of amino acids [8, 12]. The

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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

192 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 on-line ultra-pure bicarbonate-based dialysate (n= 26). All patients were dialysed with low (n=109) or high-flux (n=83) polysulfone 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 January 5th, 2007.

Baseline data

Medical charts were reviewed for age, gender, weight, height, underlying renal disease, dialysis vintage, history of transplantation, diabetes mellitus, current hypertension, co-morbid conditions, past or current smoking and current medication. Existence of hypertension was defined by pre-dialysis blood pressure higher or equal to 140/90mmHg and/or by a current antihypertensive 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 automat 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).

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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 (m^2). The creatinine index (CI) was computed from creatinine kinetic modelling as described previously. Briefly, CI was deducted from creatinine generation rate using a single pool variable volume model [14, 18] according to the following formula :

CI (mg/kg/day) = 162.7 x G_{Cr}/BW_{post} + 0.00429 x $TAC_{Cr}lm$

with G_{Cr} = Creatinine generation rate, BW_{post} = post dialysis weight,

$TAC_{Cr}lm$ = logarithmic mean-based, time-averaged creatinine concentration.

Follow-up period and End point

Patients were followed yearly during 5 years. They were not significantly modified in term of dialysis treatment and schedules during this follow-up period. Each year, during five 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:

- Cardiovascular events (myocardial infarction, congestive heart failure and sudden death)

- Non cardiovascular events (infection, neoplasm, other and unknown causes).

Statistical analysis

Descriptive statistics are presented as percentages for categorical variables, as means with s.e.m. 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 3 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 (5 values of HDL cholesterol because of triacylglycerols 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

187 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 averaged Kt/V was 1.47 ± 0.02. History of smoking, diabetes and current hypertension respectively represents 26.2%, 20.3% and 22.5% of the population. No significant difference was observed in nutritional markers such as albumin, transthyretin, muscle mass estimation from creatinine kinetic modelling,

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inflammation or lipid parameters according to dialysis method (standard HD or hemodiafiltration).

89 deaths occurred during the five year-follow-up, corresponding to a 9.5% annual mortality rate. 53 (59.6%) of these deaths had a cardiovascular cause and 36 (40.4%) a non cardiovascular cause (14 infections, 7 neoplasm, 7 cachexia and 8 miscellaneous causes).

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). By 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 according 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 predialytic 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 additive in predicting poor outcome in HD patients in all cause as well as in cardiovascular mortality.

Multivariate analysis

Table 2 describes the proportional hazards model using all of the parameters which were significantly associated with mortality in the previous analysis, which includes CRP, transthyretin, CI (which is more predictive than predialysis 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). By contrast, CI was significantly associated with all cause and CV mortality [RR=2.19 [1.10-4.35], p=0.0251; RR=2.61 [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 HD population [1]. Our results confirm previous observations showing that

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transthyretin is an independent determinant of mortality in HD patients. In addition, we showed in this study that muscle mass determination by creatinine index derived from creatinine modelling has an additive value to transthyretin in all cause and cardiovascular 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 hypoalbuminemia. On the other hand, hypoalbuminemia 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, 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, predialysis blood urea nitrogen, creatinine, albumin, phosphorus and bicarbonate. In addition, transthyretin levels, but not albumin, are predictive of cardiovascular hospitalization. According to these data, monthly transthyretin measurement is recommended by both American and European consensus group in the nutritional assessment of dialysis patients [25, 26]. In the present study, both univariate and multivariate analyses underline transthyretin as a more powerful

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predictor of all cause mortality in HD population [27] 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 relative 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 which 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 Kt/V of 1.47$\pm$0.02), with less than 1/3 of patient lower than the nutrition K DOQI recommandations, 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

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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 [³H]-leucine [7], which are expensive and difficult to implement in clinical practice.

By 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 which 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 predialysis 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 creatinine index and tranthyretin are maintained over time from two to five years of follow up (**Figure 4**). Secondly, multivariate analysis shows that CI and transthyretin are independent, and therefore additive risk factors for all cause and also for cardiovascular mortality (**Figure 3**). Sarcopenia in stable HD patients is another expression of the malnutrition inflammation complex syndrom that should be defected 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 dyslipidemia, high BMI or hypertension) become protective factors for CV morbidity in 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-O.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 trigyceride levels. In this long term follow-up study, CRP levels, adjusted for age, gender, dialysis vintage, diabetes, smoking and hypertension appears as a predictive risk factor for overall and non cardiovascular mortality but not for cardiovascular 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 cardiovascular mortality reaches significance (RR=2.053 [1.061-3.974], p=0.0327) in agreement with previous studies [2, 5, 9, 10, 15]. The key role of inflammation in hemodialysis-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 dyslipidemia. Uremic 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 transthyretin, as a reliable index of visceral protein, and creatinine index, 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 transthyretin 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.

Aknowledgements

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	All causes			Cardiovascular causes			Non cardiovascular causes		
	RR	**[IC à 95 %]**	**P**	**RR**	**[IC à 95 %]**	**P**	**RR**	**[IC à 95 %]**	**P**
CRP (mg/l)									
- <4.21	1			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
- ≥ 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
Transthyretin (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
- ≥ 0.31	1			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
- ≥ 39.06	1			1			1		
BMI (Kg/m^2)									
- <21.24	1			1			1		
- [21.24-25.27[	1.24	0.71-2.14	NS	1.34	0.66-2.76	NS	1.10	0.46-2.59	NS
- ≥ 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	1			1			1		
- [4.37-5.52[	0.96	0.59-1.59	NS	1.15	0.60-2.22	NS	0.75	0.34-1.62	NS
- ≥ 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
Triacylglycerols (mmol/l))									
- <1.34	1			1			1		
- [1.34-2.28[	0.59	0.34-1.01	0.0557	0.72	0.34-1.54	NS	0.44	0.20-0.98	0.0453
- ≥ 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
- ≥ 1.15	1			1			1		
LDL cholesterol (mmol/l)									
- <2.42	1			1			1		
- [2.42-3.34 [	0.76	0.46-1.25	NS	0.72	0.38-1.38	NS	0.82	0.38-1.80	NS
- ≥ 3.34	0.37	0.20-0.66	0.0008	0.37	0.17-0.80	0.0121	0.36	0.14-0.88	0.0248
Vitamine E (µmol/l)									
- <26.2	1			1			1		
- [26.2-34.4[	0.51	0.31-0.85	0.0099	0.66	0.34-1.29	NS	0.35	0.16-0.80	0.0122
- ≥ 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
Adjusted Vitamine E (µmol/mmol)									
- <4.13	1			1			1		
- [4.13-4.77[	1.20	0.72-2.00	NS	1.01	0.51-1.99	NS	1.46	0.67-3.19	NS
- ≥ 4.77	0.88	0.52-1.50	NS	0.80	0.41-1.59	NS	0.95	0.40-2.25	NS
Predialytic creatinine (µmol/l/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
- ≥ 852	1			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
- ≥ 18.9	1			1			1		

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

	All causes			Cardiovascular			Non cardiovascular		
	RR	**[IC à 95%]**	**P**	**RR**	**[IC à 95%]**	**P**	**RR**	**[IC à 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
- ≥ 0.31	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
- ≥ 18.9	1			1			1		
Total cholesterol (mmol/l))									
- <4.37	1			1			1		
- [4.37-5.52[	1.24	0.71-2.15	NS	1.56	0.73-3.33	NS	0.91	0.40-2.07	NS
- ≥ 5.52	0.69	0.37-1.26	NS	0.82	0.36-1.84	NS	0.56	0.22-1.44	NS
CRP (mg/l)									
- <4.21	1			1			1		
- [4.21-12.58[	0.89	0.47-1.68	NS	0.70	0.30-1.64	NS	1.08	0.40-2.87	NS
- ≥ 12.58	1.42	0.78-2.59	NS	1.26	0.57-2.76	NS	1.45	0.57-3.71	NS
Gender									
- Men	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		
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		
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		
Yes	1.71	0.99-2.94	0.0550	2.52	1.28-4.97	0.0076	0.81	0.30-2.22	NS

Table 2 : Final multivariate cox proportional-hazards analysis of factors predicting all-cause, cardiovascular and non cardio vascular mortality among hemodialysis patients adjusted for age, gender, dialysis vintage, diabetes, smoking and hypertension.

Legends to figures

Figure 1. Survival curve of hemodialysis patients according to transthyretin tertiles; all cause deaths

Figure 2. Survival curve of hemodialysis patients according to creatinine index tertiles; all cause deaths

Figure 3. Creatinine index and transthyretin : additive predictive markers of all cause (panel A) and cardiovascular (panel 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, 12 for low, median and high transthyretin values respectively. High creatinine index ($\geq$ 15.2), n= 32, 32, 61 for low, median and high transthyretin values respectively.

Figure 4. Creatinine index and transthyretin as predictive markers of mortality : trends in relative risks over time.

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