Nutritional status in chronic dialysis patients : associations with development of disease and survival

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Excess mortality due to interaction between protein-energy wasting, inflammation and cardiovascular disease in chronic dialysis patients

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ABSTRACT

Background Protein-energy wasting, inflammation and cardiovascular diseases (CVD) clearly contribute to the high mortality in chronic dialysis. Our aim was to examine the presence of additive interaction between these three risk factors in their association with long-term mortality in dialysis patients.

Methods Patients from a prospective multi-centre cohort study among ESRD patients starting with their first dialysis treatment (the Netherlands Cooperative Study on the Adequacy of Dialysis-2 [NECOSAD-II]) with complete data on these risk factors were included (n=815, age: 59 ± 15 years, 60% men, 65% HD). Hazard ratios (HR) were calculated for all-cause mortality in 7-years of follow-up. The presence of interaction between the three risk factors was examined, based on additivity of effects.

Results Of all patients, 10% only suffered from protein-energy wasting (1-5 on the 7-point subjective global assessment), 11% from inflammation (CRP≥10 mg/L), 14% from CVD and 22% had any combination of two components. Only 6% of the patients had all three risk factors. Patients with either protein-energy wasting (HR1.6; 95% CI 1.3 to 2.0), inflammation (HR 1.6; 95% CI 1.3 to 2.0), or CVD (HR 1.7; 95% CI 1.4 to 2.1) had an increased mortality risk. In patients with all three risk factors, the crude mortality rate of 45 per 100 person-years was 16 deaths per 100 person-years higher than expected from the addition of the solo effects of protein-energy wasting, inflammation and CVD. The relative excess risk due to interaction was 2.9 (95% CI 0.3 to 5.4), implying additive interaction. After adjustment for age, sex, treatment modality, primary kidney diseases, diabetes and malignancy the HR for patients with all three risk factors was 4.8 (95% CI 3.2 to 7.2).

Conclusions The concurrent presence of protein-energy wasting, inflammation and CVD increased the mortality risk strikingly more than expected, implying that protein-energy wasting interacts with inflammation and cardiovascular diseases in dialysis patients.

INTRODUCTION

Despite continuous improvements in dialysis therapies and the addition of several novel classes of pharmacotherapy during the last 20 years, the mortality of end-stage renal disease (ESRD) patients remains alarmingly high world-wide,[1] with an annual mortality of about 20%.[2;3] Patients with ESRD suffer from multiple traditional cardiovascular risk factors that are associated with mortality, such as hypertension, insulin resistance, dyslipidemia and atherosclerosis.[4] However, these factors do not completely explain the increased mortality risk.[5;6]

The observation that both protein-energy malnutrition and systemic inflammation are highly prevalent in patients with ESRD, and are associated with a substantially increased mortality risk, has generated much interest.[7-9] Signs of malnutrition and chronic inflammation have been reported in 30 and 60% of European dialysis patients.[10-12] Since malnutrition, inflammation and atherosclerotic cardiovascular diseases (CVD) often coexist,[13] these risk factors have been proposed to be pathophysiologically linked.[14;15] Their combination has previously been referred to as the malnutrition, inflammation and atherosclerosis (MIA) syndrome.[16]

Recently, an expert panel suggested the term protein-energy wasting (PEW) instead of malnutrition to indicate the presence of abnormalities in protein-energy nutritional status in the dialysis population, which often goes beyond an inadequate intake in these patients.[9;17] Although it has become apparent that many of the measures indicating the presence of a malnourished condition can also be induced by inflammatory processes[17] and although many studies have shown associations between either PEW, inflammation or CVD with mortality,[7-9;18;19] the presence of interaction between these three risk factors in relation to outcome has not been addressed before. In general, interaction between risk factors occurs whenever the effect of one is dependent on the presence of another risk factor.[20] Additive interaction between the three risk factors would be present when the mortality in patients with all three risk factors would be higher than expected based on the addition of the solo effects of the three risk factors. If PEW, inflammation and CVD are biologically independent risk factors, no interaction will be found. On the other hand, the presence of interaction between the three risk factors would support the existence of a syndrome.

Therefore, the objective of the present study was to examine the separate mortality risks of PEW, inflammation and CVD, as well as the presence of additive interaction between these three risk factors in their association with long-term mortality. To that end, we used the Netherlands Cooperative Study on the Adequacy of Dialysis-2 (NECOSAD-II) Study, a prospective cohort of incident dialysis patients in The Netherlands.

SUBJECTS AND METHODS

Subjects

Patients with ESRD of at least 18 years of age and starting with their first renal replacement therapy were eligible for inclusion in NECOSAD-II. The medical ethical committees of all participating dialysis centres approved the study and all participants gave their written informed consent before inclusion. Compared with data from the Dutch Renal Replacement Registry (RENINE), this cohort forms a representative sample of all incident dialysis patients in The Netherlands.[21;22] For the present analysis, all patients who started chronic dialysis treatment between February 1997 and September 2001 and from whom a blood sample was taken at three months after the start of dialysis were eligible (n=856).

Study design

NECOSAD-II is a prospective observational cohort study that has been performed since 1997 in 38 dialysis centres in The Netherlands. Incident dialysis patients fulfilling inclusion criteria were enrolled in this study. Three months after the start of dialysis was considered as the baseline of the study. At 3 months after the start of dialysis, blood samples had been taken for routine hospital measurements, and additional serum aliquots had been frozen and stored for future analyses. Dates and causes of mortality were immediately reported during follow-up. The survival time was defined as the number of days between 3 months after the start of the dialysis treatment (baseline) and the date of death or the date of censoring due to loss to follow-up (kidney transplantation or transfer to a non-participating dialysis centre), the end of the follow-up at January 1 2007 or at a set maximum of seven years.

Data collection

All data collection in each dialysis centre was performed by two or three research nurses who were especially appointed for NECOSAD-II. At three common trainings in The Netherlands, all trial nurses were trained to collect the data according to standardized procedures. Baseline demographic data and clinical data such as age, sex, body mass index, ethnicity, primary kidney disease and comorbidity were recorded in the patient files. Primary kidney diseases and causes of death were classified according to the coding system of the European Renal Association – European Dialysis and Transplantation Association.[23]

At the same day a blood sample was taken prior to a dialysis session and urine was collected during the interdialytic interval. Renal function was calculated from the mean of creatinine and urea clearance, adjusted for body surface area (ml/min/1.73 m^2) and expressed as the residual glomerular filtration rate (rGFR). The estimated protein equivalent of nitrogen appearance (PNA) was calculated according to Bergström *et al.* and normalized to standard body weight to obtain nPNA.[10;24]

Protein-energy wasting

Nutritional status at the baseline of the study was assessed with the 7-point subjective global assessment (SGA), a modification of the SGA originally described by Detsky *et al.*.[25;26] that has been validated in NECOSAD-I.[27] Trained research nurses of the dialysis centres scored patients' recent weight change, appetite, dietary intake and symptoms of gastro-intestinal distress, and a visual assessment of loss of subcutaneous fat mass and muscle atrophy according to a standardized protocol. Based on the scores of these subscales, the research nurses appointed the SGA classification of 1 to 7, 1-3 indicating severe protein-energy wasting, 4-5 moderate protein-energy wasting and 6-7 a normal nutritional status [26;27]. For this study, the presence of protein-energy wasting at baseline was defined as a score of 1 to 5 on the 7-point SGA scale.

Inflammation

In January 2002, the serum concentration of C-reactive protein (CRP) at baseline was determined in the stored blood samples at a central laboratory using a commercial immunoturbidimetric assay with a detection limit of 3 mg/l. The between assay coefficient of variation (CV) was 1.8%. The within-run CV was 1.8%, run-to-run CV 1.7%, and day-to-day CV 2.8%. The presence of inflammation in the dialysis population was defined as a serum concentration of CRP of ≥10 mg/L.[28]

Cardiovascular diseases

Comorbidity was defined as the presence of nonrenal diseases as reported by the patients' nephrologists at the time of inclusion or in the medical history of the patients. The presence of cardiovascular comorbidity at baseline was defined as having one or more of the following clinical diagnoses: angina pectoris, previous myocardial infarction, congestive heart failure, previous cerebrovascular incident or overt peripheral vascular disease.

Concurrent presence of protein-energy wasting, inflammation and CVD

Each patient was assigned to one of eight possible categories that indicated whether patients suffered from none of these three risk factors, from PEW, inflammation or CVD alone, from one of the three possible combinations of two risk factors, or from the combination of all three risk factors at the same time. Furthermore, the patients were given a summary score to reflect whether patients suffered from no risk factors (0), any one out of three risk factors (1), any combination of two out of three (2), or the concurrent presence of all three risk factors at baseline (3).

Statistical analysis

Baseline characteristics at 3 months after the start of dialysis were expressed as mean with standard deviation (SD) or as proportion per eight possible combinations of the three risk factors.

First, we studied relative mortality risks associated with the baseline presence of PEW, inflammation, or CVD separately, compared to patients without the relevant component. Cox regression analysis was used to calculate hazard ratios (HR, equivalent to relative risks of mortality) with 95%-confidence intervals. Each of the three analyses was adjusted for age, sex, treatment modality, primary kidney disease, diabetes, malignancy, and the other two risk factors.

Second, we calculated the absolute mortality rates for all possible combinations of the three risk factors in the dialysis population, using the variable with eight categories. The mortality rate in the category without any risk factor is the background risk. The solo effect of each separate risk factor was calculated by subtracting the background risk from the observed mortality rate of each risk factor. The expected mortality rates of the possible combinations of the risk factors were then calculated by adding the background risk with the observed solo effects of PEW, inflammation and/or CVD. The interaction effect of the relevant risk factors was calculated as the difference between the expected and observed mortality rates of the combinations of the risk factors.

Finally, we examined the presence of interaction between the three risk factors in the association with mortality, using the summary score with four categories. Observed survival for each of the four categories was computed by the Kaplan-Meier method. Hazard ratios with 95%-confidence intervals were calculated for the presence of any one out of three risk factors, any combination of two out of three or the concurrent presence of all three risk factors at baseline, compared with the background risk. An interaction effect was defined as departure from causal additivity of effects, according to Rothman.[20]According to this concept, independent risk factors adhere to an additive model, indicating that interaction results in departure from additivity of rates or risks.[20] Assuming additivity, we predicted the risk ratio that would occur under causal independence for those exposed to all three risk factors by the addition of the background risk of patients without any of the three risk factors (=1; the reference category), with the solo effect of having any one risk factor, and the solo effect of any two risk factors. We then calculated the difference between this expected hazard ratio and the observed hazard ratio that was associated with the concurrent presence of all three risk factors. This difference is referred to as the relative excess risk due to interaction (RERI).[33] The 95%-

confidence interval of the RERI was calculated as proposed by Hosmer and Lemeshow.[29] We also calculated the RERIs for each combination of two risk factors. The analyses were adjusted for age, sex, primary kidney disease, treatment modality, diabetes and malignancy. We used SPSS 14.0 for Windows (SPSS, Chicago, IL) for all analyses.

RESULTS

Patient characteristics

In 856 included patients who started dialysis treatment between February 1997 and September 2001 blood samples were collected at 3 months after the start of dialysis. Serum CRP concentrations could be determined in 842 patients. In addition, in 24 patients the SGA at 3 months was missing, and in 3 patients information on the presence of comorbid conditions was missing. Thus, 815 patients (487 men and 328 women) were included in the present analysis with a mean age (± SD) of 59 (± 15) years, a mean BMI of 24.6 (± 4.1) kg/m^2, and 65% starting hemodialysis treatment. The 41 patients who were not included in our analyses due to missing data at baseline were older than the patients in the study population (65 ± 17 years). Other baseline characteristics as sex, BMI, nPNA, rGFR, primary kidney disease, and dialysis therapy were similar in both groups. The main causes of chronic kidney diseases were diabetes mellitus in 15% of the patients, glomerulonephritis in 13% and renal vascular diseases in 18%. The median follow-up of patients from 3 months until a maximum of seven years on dialysis was 2.6 years (25th, 75th-percentiles: 1.3, 4.3). During follow-up, 354 patients died, 161 (45%) due to CVD. Furthermore, 257 patients left the study because of a kidney transplantation. Other reasons for censoring during follow-up included recovery of renal function (n=6), transfer to a non-participating dialysis centre (n=27), refusal of further participation (n=81) or other (n=11). The remaining 79 patients were censored at the end of the study. Patient characteristics by the eight possible combinations of the three risk factors at baseline are shown in Table 1.

Table 1. Patient characteristics of 815 ESRD patients at 3 months after the start of chronic dialysis treatment per risk factor combination

Variable[1]	Risk factor combinations							
	None	PEW	I	CVD	PEW+I	PEW+CVD	I+CVD	PEW+I +CVD
Case mix								
N (%)	306 (38)	79 (10)	90 (11)	110 (14)	56 (7)	44 (5)	84 (10)	46 (6)
Age (y)	53 ± 15	57 ± 17	58 ± 14	62 ± 11	63 ± 15	69 ± 10	68 ± 9	68 ± 9
Sex (% men)	57	58	48	66	50	68	77	61
BMI (kg/m^2)	25.0 ± 3.8	23.0 ± 3.8	25.8 ± 4.7	24.5 ± 3.4	23.3 ± 6.0	22.6 ± 2.8	26.0 ± 3.9	24.1 ± 3.8
rGFR (mL/min/1.73 m^2)	3.9 ± 2.6	3.2 ± 2.7	3.4 ± 2.5	4.9 ± 3.4	2.9 ± 2.9	3.5 ± 2.5	3.6 ± 2.3	2.2 ± 2.3
Primary kidney disease (%)								
Diabetic nephropathy	10	10	11	32	9	21	16	20
Glomerulonephritis	16	17	17	11	13	2	7	0
Renal vascular disease	11	11	10	19	16	36	39	39
Treatment modality (% HD)	56	68	60	62	75	73	79	87
Diabetes Mellitus	14	17	16	36	16	36	24	28
Malignancy	7	9	8	7	14	7	10	15
Nutritional status								
Well-nourished (% SGA 6-7)	100	0	100	100	0	0	100	0
Mild malnutrition (% SGA 4-5)	0	87	0	0	88	89	0	78
Severe malnutrition (% SGA 1-3)	0	13	0	0	13	11	0	22
nPNA (g/kg/d)	1.03 ± 0.24	1.06 ± 0.23	1.00 ± 0.19	1.04 ± 0.20	0.95 ± 0.23	1.01 ± 0.21	0.94 ± 0.19	0.90 ± 0.17
Inflammatory status								
CRP>10 mg/L (%)	0	0	100	0	100	0	100	100
CRP (mg/L)	4.2 ± 1.9	4.1 ± 1.9	22.5 ± 22.6	4.2 ± 1.8	32.2 ± 30.3	4.6 ± 2.0	28.8 ± 43.8	51.3 ± 48.5
Cardiovascular diseases (%)	No	No	No	Yes	No	Yes	Yes	Yes
Previous cerebrovascular incident				26		23	19	24
Overt peripheral vascular disease				39		27	43	48
Coronary heart disease				66		75	73	74
Angina pectoris				33		21	35	35
Previous myocardial infarction				31		30	36	26
Congestive heart failure				21		50	26	41

[1]Values expressed as percentages or mean ± SD

PEW=Protein-energy wasting, I=Inflammation, CVD=Cardiovascular diseases, rGFR=residual Glomerular filtration rate corrected for body surface area, HD=Hemodialysis treatment, SGA=Subjective global assessment of nutritional status, nPNA= Protein nitrogen appearance normalized for actual body weight, CRP=C-reactive protein

With an increasing number of risk factors at baseline, patients were older and started more often on hemodialysis treatment. Patients with CVD were more often men and had more often had diabetes, whereas patients with inflammation more often suffered from malignancy.

Mortality risks of protein-energy wasting, inflammation and cardiovascular diseases

According to our definitions, 225 patients (28%) suffered from PEW, 276 patients (34%) suffered from inflammation and 284 patients (35%) suffered from CVD at baseline. PEW (HR 1.6; 95% CI 1.3 to 2.0), inflammation (HR 1.6; 95% CI 1.3 to 2.0), and cardiovascular diseases (HR 1.7; 95% CI 1.4 to 2.1) were each independently associated with increased risks of all-cause mortality after adjustment for age, sex, primary kidney disease, treatment modality, diabetes, malignancy, and for the other two risk factors (Table 2).

Table 2. Relative risks of all-cause mortality (hazard ratio [HR] with 95%-confidence interval) associated with the presence of protein-energy wasting, inflammation and cardiovascular diseases at three months after the start of chronic dialysis treatment in 815 dialysis patients during 7 years of follow-up

		HR (95%-CI)[1]		
Risk factor[2]	N (%)	Univariate	Models 1[3]	Model 2[4]
Protein-energy wasting (SGA 1-5)	225 (28)	2.0 (1.6-2.5)	1.6 (1.3-2.0)	1.6 (1.3-2.0)
Inflammation (CRP>10 mg/L)	276 (34)	1.9 (1.5-2.3)	1.8 (1.4-2.2)	1.6 (1.3-2.0)
Cardiovascular diseases[5]	284 (35)	2.5 (2.1-3.1)	1.8 (1.4-2.2)	1.7 (1.4-2.1)

[1]Patients without the relevant risk factor are the reference
[2]SGA=Subjective global assessment of nutritional status, CRP=C-reactive protein
[3]Three models adjusted for age, sex, primary kidney disease, treatment modality, diabetes and malignancy
[4]One model additionally adjusted for the other two risk factors
[5]Cardiovascular diseases include diagnoses of a previous cerebrovascular incident, overt peripheral vascular disease, and/or coronary heart disease

Prevalence of protein-energy wasting, inflammation and CVD

The overlap of the presence of the three risk factors in this cohort of dialysis patients is shown in Figure 1. Of all patients at baseline, 38% had no risk factor, 10% suffered from protein-energy wasting only, 11% suffered from inflammation only, 14% had only cardiovascular diseases and 22% of the patients had any combination of two risk factors. Only in 6% of the patients were all three risk factors concurrently present.

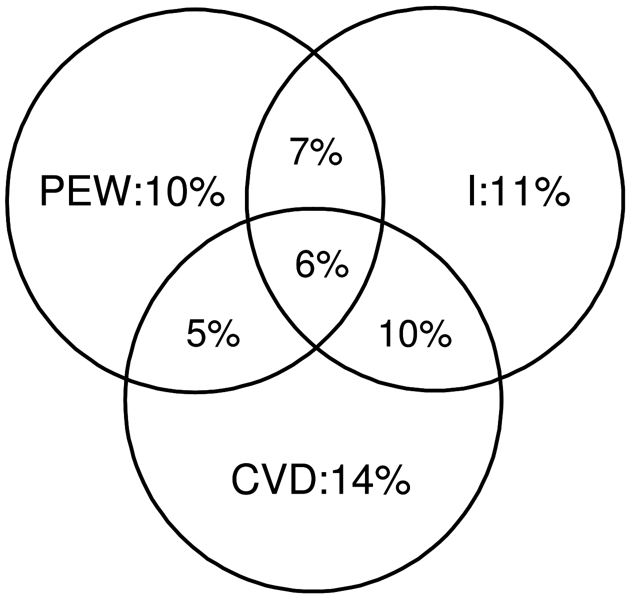


Figure 1. The presence of protein-energy wasting, inflammation, cardiovascular diseases, as well as all possible combinations in a cohort of 815 ESRD patients at 3 months after the start of chronic dialysis treatment. PEW= protein-energy wasting (SGA 1-5), I=Inflammation (CRP>10 mg/L), CVD=Cardiovascular disease. Outside the figure are 38% of the patients without any of these three risk factors at baseline. The percentages add up >100% because of rounding.

Absolute mortality rates

The crude absolute mortality rates of the dialysis patients increased with increasing number of risk factors at baseline (Table 3). Adding the background risk (7 per 100 person-years) together with the solo effects of PEW, inflammation and CVD yielded the expected mortality rates for all possible combinations of the risk factors (Table 3). In each category of patients having two risk factors, the mortality rates were 2 to 3 deaths per 100 person-years higher than expected from the addition of the solo effects of the two separate risk factors. In patients with the concurrent presence of all three risk factors, the expected mortality rate was 29 per 100 person-years. The observed mortality rate of 45 per 100 person-years was thus 16 deaths per 100 person-years higher than expected from the solo effects of PEW, inflammation and CVD.

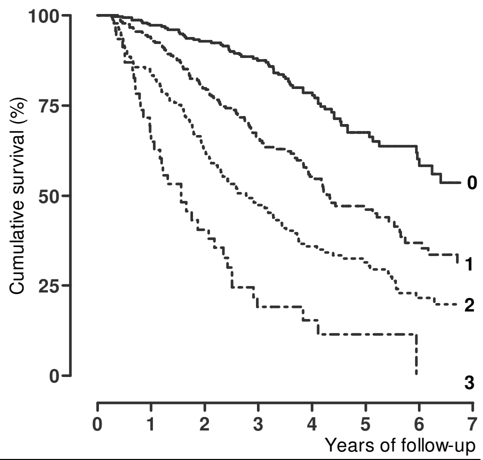
Table 3. Observed and expected absolute mortality rates, and the interaction effect, assuming additivity, per risk factor combination at three months after the start of chronic dialysis treatment in 815 dialysis patients during 7 years of follow-up

	Risk factor combinations[1]							
	None	PEW	I	CVD	PEW+I	PEW+CVD	I+CVD	PEW+I +CVD
Person-years	1023	234	273	331	172	116	225	84
Number of deaths	72	33	29	60	36	31	55	38
Per 100 py								
Mortality rates[2]	7	14	11	18	21	27	24	45
Solo effect		7	4	11				
Expected rates[3]					18	25	22	29
Interaction effect[4]					3	2	2	16

[1]PEW=Protein-energy wasting, I=Inflammation, CVD=Cardiovascular diseases, py=Person-years
[2]The category without any risk factor (None) is the background risk (7/100 py)
[3]The expected mortality rates for each combination of risk factors were calculated by adding the background risk to the solo effects of protein-energy wasting (PEW), inflammation (I) and cardiovascular diseases (CVD)
[4]The interaction effect is the difference between the observed and expected mortality rates

Relative mortality risks

For a more straightforward interpretation of the presence of interaction between all three risk factors, we grouped the eight categories used in Table 3 into a summary score of four categories. The all-cause mortality during 7 years of follow-up was 51% in the group without any risk factor, 71% in the group with any one risk factor, 81% in the group with any two risk factors, and 96% mortality in the patient group with the concurrent presence of all three risk factors (Figure 2). The HR that was expected under causal independence for those exposed to all three risk factors was calculated as the addition of the background risk (1), with the solo effect of having any one risk factor (2.1-1), and the solo effect of any two risk factors (3.5-1) (Table 4), resulting in 4.6. Compared with patients without any risk factor, patients with the concurrent presence of all three risk factors had a crude hazard ratio of 7.5 (95% CI 5.0 to 11.1) (Table 4). The RERI, defined as the difference between the expected and observed hazard ratio was 2.9 (95% CI 0.3 to 5.4) (Table 4).



No		0	1	2	3	4	5	6	7
0	NR	306	267	212	163	110	69	38	24
	ND	8	11	11	15	15	7	5	
1	NR	279	238	176	118	83	51	26	17
	ND	18	31	28	18	13	10	4	
2	NR	184	147	100	70	46	35	18	13
	ND	30	36	23	16	5	10	2	
3	NR	46	29	16	7	4	3	1	
	ND	16	10	8	1	1	2		

Figure 2. Kaplan-Meier cumulative survival during 7 years of follow up of 815 ESRD patients receiving chronic dialysis treatment, divided into four groups of having no (0), one (1), any combination of two (2), or all three risk factors (3) at baseline. No=Number of risk factors, NR=number of patients at risk, ND=number of deaths.

The RERIs of each combination of two risk factors, calculated from the crude HRs associated with the risk factors, were 0.4 (95% CI -0.5 to 1.3) for PEW and inflammation, 0.5 (95% CI -0.5 to 1.6) for inflammation and CVD and 0.9 (95% CI -0.5 to 2.2) for PEW and CVD.

After adjustment for age, sex, primary kidney disease, treatment modality, diabetes and malignancy, the HR that was associated with the concurrent presence of all three risk factors was 4.8 (95% CI 3.2 to 7.2) (Table 4).

Table 4. Crude and adjusted hazard ratios (HR, with 95%-confidence interval) of 7-years all-cause mortality, associated with any one risk factor, any combination of two risk factors, or the concurrent presence of protein-energy wasting, inflammation and CVD, compared to no risk factors at three months after the start of chronic dialysis treatment in 815 dialysis patients

Model		HR (95%-CI)[1]				
		None	1	2	3	RERI[2] (95%-CI)
1	Crude model	1	2.1 (1.6-2.8)	3.5 (2.6-4.8)	7.5 (5.0-11.1)	2.9 (0.3-5.4)
2	1+ Age, sex, mod	1	1.9 (1.4-2.5)	2.5 (1.9-3.4)	5.1 (3.4-7.6)	-
3	2+ PKD, DM, malignancy	1	1.8 (1.4-2.5)	2.5 (1.9-3.4)	4.8 (3.2-7.2)	-

[1]None=none, 1=one, 2=any combination of two, 3=all three risk factors at baseline, +=model noted additionally adjusted for, mod=Treatment modality, PKD=Primary kidney disease, DM=Diabetes mellitus
[2]RERI=Relative excess risk due to interaction; A RERI of 0 would indicate that protein-energy wasting, inflammation and cardiovascular diseases are causally independent; a RERI of 2.9 means that because of interaction between the three risk factors, the hazard ratio is 2.9 greater than expected from the addition of the solo effects of three risk factors. After adjustment for confounders in the multiplicative Cox regression model, a RERI can not be interpreted and is therefore not given for the adjusted models.

DISCUSSION

We investigated whether protein-energy wasting, inflammation and CVD prospectively interact in the association with long-term mortality in a cohort of incident dialysis patients, thereby resulting in a syndrome that leads to higher mortality. A small proportion of the patients suffered from all three risk factors at baseline. Interestingly, these patients had a fivefold increased mortality risk, compared with patients without any risk factor. Moreover, there was a substantial interaction between the three risk factors in their association with mortality, resulting in 16 deaths per 100 person-years more in patients with all three risk factors than expected on the basis of the solo effects of PEW, inflammation and CVD.

Protein-energy wasting is a widely known risk factor of mortality in patients with ESRD,[30-32] and the presence of accelerated vascular ageing and a high mortality due to CVD in patients with renal disease has been described as early as 1969.[33] Inflammation has more recently been found to increase the mortality risk in patients with ESRD.[18;19] In addition to these previous findings, we showed that PEW, inflammation and CVD each remained an independent risk factor after adjustment for the other two risk factors. Furthermore, our study extended earlier findings[18;34] by showing that all together the three independent risk factors interacted in their association with mortality. In contrast, there was no significant interaction between each two risk factors, implying that indeed all three risk factors are necessary to result in the large overall interaction effect of 16/100 person-years.

We found a small proportion of 6% of the patients with the concurrent presence of PEW, inflammation and CVD in our population, compared with 22% in a predialysis population and 23% in a study of 128 prevalent hemodialysis patients.[15;18] One of the possible explanations for the discrepancy with these studies is the definition used for CVD. In the predialysis patients, carotid plaques were measured with ultrasonography,[15] whereas in the present study we used the clinical diagnoses of cardiovascular diseases. Thus, we may have underestimated the true prevalence of atherosclerotic CVD. On the other hand, the clinical diagnoses of CVD are readily available for identification of high-risk patients, whereas ultrasonography is not routinely performed in current clinical practice. Another study in the Swedish ESRD population reported that 34% had clinical CVD at start of dialysis as defined by medical history,[35] which is in perfect agreement with the total of 35% of patients with CVD in our population. Therefore, our clinical data seem valid.

A few considerations are important in the interpretation of our results. First, with the definitions used in our study, we tried to disentangle the contributions of PEW and inflammation to mortality. However, a single CRP concentration may not be the most appropriate method to define the presence of chronic inflammation. Hence, inflammation may be present in patients with a CRP concentration below 10 mg/L in our study. Nevertheless, any misclassification that may have occurred because of the definitions may have diluted present interaction effects. Thus in case of misclassification, the true interaction effect would have been larger than the effect we detected in the present analysis. Second, with an increasing number of risk factors at baseline, the severity of the risk factors increased as well, which may have contributed to the higher mortality. However, any pathophysiological enhancement between PEW, inflammation and CVD may be considered as additional evidence for the existence of a syndrome.

The present analysis focused on the baseline information about the risk factors, while during time on dialysis treatment more risk factors may develop. Future longitudinal research must indicate whether patients with one or two risk factors have an increased risk of developing a second or the third risk factor during dialysis, which may affect subsequent mortality. This would prospectively proof the development of a syndrome between PEW, inflammation and CVD during time on dialysis.

We examined the presence of additive interaction using Cox regression analysis, which is a statistically multiplicative model. The RERI, assuming additivity, can be determined from this model.[20] In our study, the crude HR that was associated with the concurrent presence of PEW, inflammation and CVD was significantly 2.9 (95% CI 0.3 to 5.4) greater than expected from the addition of the solo effects of the risk factors. After adjustment for possible confounders on a multiplicative scale the RERI that is calculated from the adjusted HRs is difficult to interpret.[36] Therefore, we also calculated the synergy index, a measure of interaction that does not vary across strata.[36] The synergy index, which should be interpreted as the excess risk from exposure when there is interaction relative to the excess risk from exposure without interaction, was 1.8 (95% CI 1.2 to 2.8) in the crude model and 1.6 (95% CI 1.0 to 2.7) in the adjusted model, implying that the interaction effect was robust.

In determining an interaction effect, the present study aimed to translate epidemiological observations into evidence for the existence of a syndrome, where the whole is more than its parts. Several theories have been proposed to explain the supposed links between PEW, inflammation and CVD, but the pathophysiological mechanisms involved remain unclear.[7;8;37] Inflammation, mediated by pro-inflammatory cytokines, may predispose to both PEW and CVD in end-stage renal disease.[15] Cytokines have been shown to mediate proteolysis in muscle, to upregulate basal metabolic rate and to inhibit appetite and food intake.[13] Atherosclerosis has been recognized to be an inflammatory disease.[38] Finally, PEW may aggravate existing inflammation and accelerate atherosclerosis.[15]

In summary, these epidemiological data support the presence of an interaction effect between PEW, inflammation and CVD, resulting in excess mortality in chronic dialysis patients. By means of regular screening, dialysis patients with an especially high mortality risk can be identified. Multiple pathophysiological pathways may underlie this interaction effect. Intervention studies directed at these pathways should be aimed at minimizing protein-energy wasting and inflammation together with cardiovascular diseases in order to reduce the alarmingly high mortality among dialysis patients.

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REFERENCES

1. Yoshino M, Kuhlmann MK, Kotanko P et al.: International differences in dialysis mortality reflect background general population atherosclerotic cardiovascular mortality. J Am Soc Nephrol 17:3510-3519, 2006
2. US Renal Data System: Excerpts from the USRDS 2006 Annual Data Report. Am J Kidney Dis [Suppl]49:S1-S296, 2007
3. van Dijk PC, Jager KJ, Stengel B et al.: Renal replacement therapy for diabetic end-stage renal disease: data from 10 registries in Europe (1991-2000). Kidney Int 67:1489-1499, 2005
4. Ma KW, Greene EL, Raij L: Cardiovascular risk factors in chronic renal failure and hemodialysis populations. Am J Kidney Dis 19:505-513, 1992
5. Cheung AK, Sarnak MJ, Yan G et al.: Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int 58:353-362, 2000
6. Longenecker JC, Coresh J, Powe NR et al.: Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. J Am Soc Nephrol 13:1918-1927, 2002
7. Kaysen GA: Association between inflammation and malnutrition as risk factors of cardiovascular disease. Blood Purif 24:51-55, 2006
8. Kalantar-Zadeh K, Stenvinkel P, Pillon L, Kopple JD: Inflammation and nutrition in renal insufficiency. Adv Ren Replace Ther 10:155-169, 2003
9. Stenvinkel P, Heimburger O, Lindholm B: Wasting, but not malnutrition, predicts cardiovascular mortality in end-stage renal disease. Nephrol Dial Transplant 19:2181-2183, 2004
10. Jansen MA, Korevaar JC, Dekker FW et al.: Renal function and nutritional status at the start of chronic dialysis treatment. J Am Soc Nephrol 12:157-163, 2001
11. Yeun JY, Levine RA, Mantadilok V, Kaysen GA: C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis 35:469-476, 2000
12. Zoccali C, Benedetto FA, Mallamaci F et al.: Inflammation is associated with carotid atherosclerosis in dialysis patients. Creed Investigators. Cardiovascular Risk Extended Evaluation in Dialysis Patients. J Hypertens 18:1207-1213, 2000
13. Avesani CM, Carrero JJ, Axelsson J et al: Inflammation and wasting in chronic kidney disease: Partners in crime. Kidney Int [Suppl]S8-S13, 2006
14. Owen WF, Lowrie EG: C-reactive protein as an outcome predictor for maintenance hemodialysis patients. Kidney Int 54:627-636, 1998
15. Stenvinkel P, Heimburger O, Paultre F et al.: Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int 55:1899-1911, 1999
16. Stenvinkel P, Heimburger O, Lindholm B, Kaysen GA, Bergstrom J: Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). Nephrol Dial Transplant 15:953-960, 2000
17. Fouque D, Kalantar-Zadeh K, Kopple J et al.: A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int 73:391-398, 2008
18. Qureshi AR, Alvestrand A, Divino-Filho JC et al.: Inflammation, malnutrition, and cardiac disease as predictors of mortality in hemodialysis patients. J Am Soc Nephrol 13:28-36, 2002
19. den Elzen WP, van Manen JG, Boeschoten EW, Krediet RT, Dekker FW: The effect of single and repeatedly high concentrations of C-reactive protein on cardiovascular and non-cardiovascular mortality in patients starting with dialysis. Nephrol Dial Transplant 21:1588-1595, 2006
20. Rothman KJ: Measuring interactions. In: Rothman KJ, ed. Epidemiology; An Introduction. Oxford University Press, Inc. New York, NY: p 168-180, 2002
21. www.renine.nl, accessed February 11, 2008.

22. ERA-EDTA Registry: ERA-EDTA Registry 2005 Annual Report. Academic Medical Center, Department of Medical Informatics, Amsterdam, The Netherlands, 2007
23. van Dijk PC, Jager KJ, de Charro F et al.: Renal replacement therapy in Europe: the results of a collaborative effort by the ERA-EDTA registry and six national or regional registries. Nephrol Dial Transplant 16:1120-1129, 2001
24. Bergstrom J, Heimburger O, Lindholm B: Calculation of the protein equivalent of total nitrogen appearance from urea appearance. Which formulas should be used? Perit Dial Int 18:467-473, 1998
25. Detsky AS, McLaughlin JR, Baker JP et al.: What is subjective global assessment of nutritional status? J Parenter Enteral Nutr 11:8-13, 1987
26. McCusker FX, Teehan BP, Thorpe KE, Keshaviah PR, Churchill DN: How much peritoneal dialysis is required for the maintenance of a good nutritional state? Canada-USA (CANUSA) Peritoneal Dialysis Study Group. Kidney Int [Suppl]56:S56-S61, 1996
27. Visser R, Dekker FW, Boeschoten EW, Stevens P, Krediet RT: Reliability of the 7-point subjective global assessment scale in assessing nutritional status of dialysis patients. Adv Perit Dial 15:222-225, 1999
28. Tsirpanlis G, Bagos P, Ioannou D et al.: Exploring inflammation in hemodialysis patients: persistent and superimposed inflammation. A longitudinal study. Kidney Blood Press Res 27:63-70, 2004
29. Hosmer DW, Lemeshow S: Confidence interval estimation of interaction. Epidemiology 3:452-456, 1992
30. Bergstrom J: Nutrition and mortality in hemodialysis. J Am Soc Nephrol 6:1329-1341, 1995
31. Combe C, Chauveau P, Laville M et al. : Influence of nutritional factors and hemodialysis adequacy on the survival of 1,610 French patients. Am J Kidney Dis 37:81-88, 2001
32. Leavey SF, Strawderman RL, Jones CA, Port FK, Held PJ: Simple nutritional indicators as independent predictors of mortality in hemodialysis patients. Am J Kidney Dis 31:997-1006, 1998
33. Friedman SA, Novack S, Thomson GE: Arterial calcification and gangrene in uremia. N Engl J Med 280:1392-1394, 1969
34. Stenvinkel P, Chung SH, Heimburger O, Lindholm B: Malnutrition, inflammation, and atherosclerosis in peritoneal dialysis patients. Perit Dial Int 21:S157-S162, 2001
35. Axelsson J, Qureshi AR, Divino-Filho JC et al.: Are insulin-like growth factor and its binding proteins 1 and 3 clinically useful as markers of malnutrition, sarcopenia and inflammation in end-stage renal disease? Eur J Clin Nutr 60:718-726, 2006
36. Skrondal A: Interaction as departure from additivity in case-control studies: a cautionary note. Am J Epidemiol 158:251-258, 2003
37. Caglar K, Hakim RM, Ikizler TA: Approaches to the reversal of malnutrition, inflammation, and atherosclerosis in end-stage renal disease. Nutr Rev 60:378-387, 2002
38. Ross R: Atherosclerosis--an inflammatory disease. N Engl J Med 340:115-126, 1999