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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 (PEW), 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 Co-operative 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 PEW (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 PEW (HR: 1.6, 95% CI: 1.3–2.0), inflammation (1.6, 1.3–2.0) or CVD (1.7, 1.4–2.1) had an increased mortality risk. In patients with all three risk factors, the crude mortality rate of 45/100 person-years was 16 deaths/100 person-years higher than expected from the addition of the solo effects of PEW, inflammation and CVD. The relative excess risk due to interaction was 2.9 (95% CI: 0.3–5.4), 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: 3.2–7.2).

Conclusions. The concurrent presence of PEW, inflammation and CVD increased the mortality risk strikingly more than expected, implying that PEW interacts with inflammation and CVD in dialysis patients.

Keywords: cardiovascular disease; chronic dialysis; inflammation; mortality risk; protein–energy wasting

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 worldwide [1], with an annual mortality of ∼20% [2,3]. Patients with ESRD suffer from multiple traditional cardiovascular risk factors that are associated with mortality, such as hypertension, insulin resistance, dyslipidaemia 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

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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, the 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 Co-operative Study on the Adequacy of Dialysis-2 (NECOSAD-II) study, a prospective cohort of incident dialysis patients in the Netherlands.

Subjects and methods

Subjects

ESRD patients 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 were eligible who started chronic dialysis treatment between February 1997 and September 2001 and from whom a blood sample was taken at 3 months after the start of dialysis ($n = 856$) 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 1 January 2007 or at a set maximum of 7 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 (BMI), 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 inter-dialytic 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. 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 seven-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 1–7: 1–3 indicating severe PEW, 4–5 moderate PEW and 6–7 a normal nutritional status [26,27]. For this study, the presence of PEW at baseline was defined as a score of 1–5 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 PEW, 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. The observed survival for each of the four categories was computed by the Kaplan–Meier method. HR 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 to 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 HR and the observed HR 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, USA) 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/m² and 65% starting haemodialysis 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 7 years on dialysis was 2.6 years (25th, 75th percentiles: 1.3, 4.3). During the 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 the 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. With an increasing number of risk factors at baseline, patients were older and started more often on

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

Variable[a]	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 (years)	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/day)	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

PEW = protein-energy wasting, I = inflammation, CVD = cardiovascular diseases, rGFR = residual glomerular filtration rate corrected for body surface area, HD = haemodialysis treatment, SGA = subjective global assessment of nutritional status, nPNA = normalized protein-nitrogen appearance, CRP = C-reactive protein.
[a]Values expressed as percentages or mean ± SD.

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 3 months after the start of chronic dialysis treatment in 815 dialysis patients during 7 years of follow-up

Risk factor	N (%)	HR (95% CI)[a]		
		Univariate	Model 1[b]	Model 2[c]
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[d]	284 (35)	2.5 (2.1–3.1)	1.8 (1.4–2.2)	1.7 (1.4–2.1)

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

haemodialysis 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 PEW, inflammation and cardiovascular diseases

According to our definitions, 225 patients (28%) suffered from PEW, 276 (34%) from inflammation and 284 (35%) from CVD at baseline. PEW (HR: 1.6, 95% CI: 1.3–2.0), inflammation (1.6, 1.3–2.0) and CVD (1.7, 1.4–2.1) 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).

Prevalence of PEW, 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 PEW only, 11% suffered from inflammation only, 14%
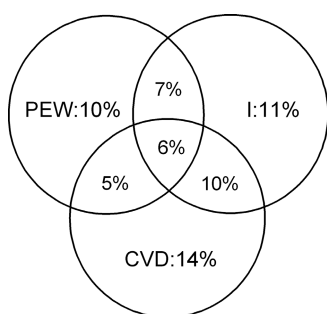
Fig. 1. The presence of protein-energy wasting, inflammation and cardio-vascular diseases, as well as all possible combinations, in a cohort of 815 ESRD patients at 3 months after the start of chronic dialysis treatment. PEW = protein-energy wasting (SGA 1–5), I = inflammation (CRP > 10 mg/L), CVD = cardiovascular disease. Outside the figure are 38% of the patients without any of these three risk factors at baseline. The percentages add up to >100% because of rounding.

had only CVD 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.

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 (7/100 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 2–3 deaths/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 29/100 person-years. The observed mortality rate of 45/100 person-years was thus 16 deaths/100 person-years higher than expected from the solo effects of PEW, inflammation and CVD.

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 to patients without any risk factor, patients with the concurrent presence of all three risk factors had a crude HR of 7.5 (95% CI: 5.0–11.1) (Table 4). The RERI, defined as the difference between the expected and observed HR, was 2.9 (95% CI: 0.3–5.4) (Table 4).

The RERIs of each combination of two risk factors, calculated from the crude HRs associated with the risk factors, were 0.4 (95% CI: −0.5–1.3) for PEW and inflammation, 0.5 (95% CI: −0.5–1.6) for inflammation and CVD and 0.9 (95% CI: −0.5–2.2) 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: 3.2–7.2) (Table 4).

Discussion

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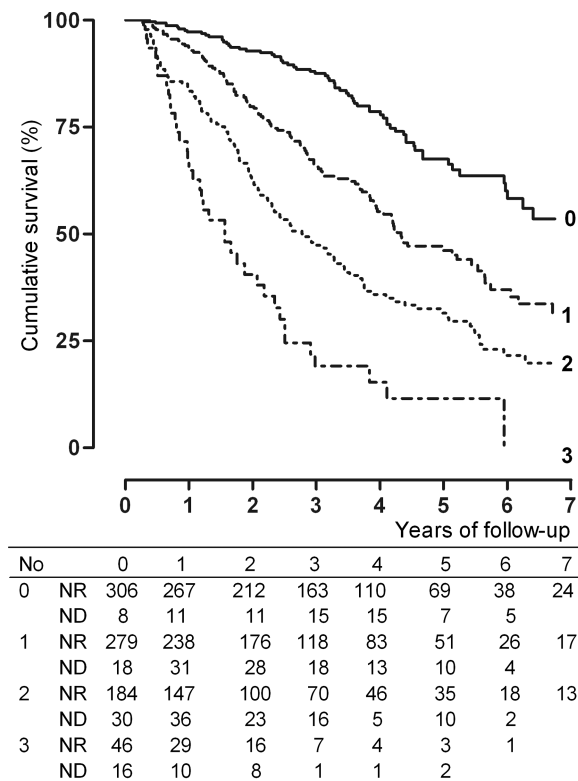
Table 3. Observed and expected absolute mortality rates, and the interaction effect, assuming additivity, per risk factor combination at 3 months after the start of chronic dialysis treatment in 815 dialysis patients during 7 years of follow-up

	Risk factor combinations							
	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[a]	7	14	11	18	21	27	24	45
Solo effect		7	4	11				
Expected rates[b]					18	25	22	29
Interaction effect[c]					3	2	2	16

PEW = Protein-energy wasting, I = inflammation, CVD = cardiovascular diseases, py = person-years
[a]The category without any risk factor (None) is the background risk (7/100 py).
[b]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).
[c]The interaction effect is the difference between the observed and expected mortality rates.

Fig. 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.

between the three risk factors in their association with mortality, resulting in 16 deaths/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.

PEW 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 to 22% in a predialysis population and 23% in a study of 128 prevalent haemodialysis 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 CVD. 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 <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 the 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.

Table 4. Crude and adjusted hazard ratios (HR, with 95% confidence interval) of 7-year 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 3 months after the start of chronic dialysis treatment in 815 dialysis patients

		HR (95% CI)				RERI (95%-CI)
Model		None	1	2	3	
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)	–

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; 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 the 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 cannot be interpreted and is therefore not given for the adjusted models.

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 prove 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 associated with the concurrent presence of PEW, inflammation and CVD was significantly 2.9 (95% CI: 0.3–5.4) 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 HR 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 (1.2–2.8) in the crude model and 1.6 (1.0–2.7) 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 ESRD [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 PEW and inflammation together with CVD in order to reduce the alarmingly high mortality among dialysis patients.

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