Chapter 3

Trimestral variation patterns of C-reactive protein, interleukin-6 and tumor necrosis factor-α are similarly associated with survival in hemodialysis patients

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Abstract

Background: The impact of intra-individual changes of inflammatory markers (other than C-reactive protein; *CRP*) on mortality in hemodialysis patients is unknown. We therefore studied survival in relation to trimestral variation of CRP, interleukin-6 (*IL-6*) and tumor necrosis factor-α (*TNF-a*).

Methods: In 201 prevalent hemodialysis patients from the Mapping of Inflammatory Markers in Chronic Kidney Disease (MIMICK) cohort, serum CRP, IL-6 and TNF-α were measured 3 months apart and survival was assessed during follow-up. Based on fluctuations along tertiles of distribution, four patterns were defined for each inflammatory marker: stable-low, decrease, increase and stable-high. Hazard ratios were calculated by the Cox proportional hazard model and Pearson's test was used to correlate changes. CRP analyses were replicated in 472 incident hemodialysis patients from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD).

Results: Patients with persistently elevated CRP values had the worst mortality in crude (HR: 2.98 [95% CI: 1.71-5.20]) and adjusted (2.79 [1.58-4.94]) Cox models, together with those who increased in their CRP levels (crude 3.27 [1.91-5.60]; adjusted 3.13 [1.79-5.45]). Similar survival patterns were observed for IL-6 and TNF-α variation categories. Correlations among these changes were, however, not strong. In the replication cohort, individuals with persistently elevated CRP values also showed the highest mortality risk (crude 3.38 [2.31-4.94]; adjusted 2.33 [1.58-3.45]).

Conclusions: Trimestral variation patterns of TNF-α, IL-6, and CRP are similarly associated with survival in hemodialysis patients. The concordance between changes of these biomarkers was low, suggesting that different pathways may trigger each of these markers.

Introduction

Patients with advanced chronic kidney disease (*CKD*) are at an increased mortality risk.[1] Understanding the pathophysiology of this excess mortality may contribute to adequate risk profiling and encourage clinical interventions. Recent attention has focused on the role of increased inflammation among advanced CKD patients in promoting progression of underlying comorbid illnesses and acting as a catalyst for other risk factors, as a consequence leading to increased mortality.[2]

The robust evidence concerning single-measurements of various inflammatory biomarkers as independent predictors of comorbidities and mortality in CKD patients has justified there use for identification of patients at increased risk.[3-5] However, few studies have until now addressed the relationship between longitudinal inflammatory variation and mortality risk.[6-9] Clinically, this translates into an uncertainty regarding how to interpret the impact of intra-individual variability of the inflammatory response on mortality. Moreover, the few studies available on this topic have only focused on C-reactive protein (*CRP*) variation. Hence, we aimed at studying the association between the pattern of changes over a 3-month period of CRP, interleukin-6 (IL-6) and tumor necrosis factor-α (*TNF-a*) and survival in two well-characterized cohorts of hemodialysis (*HD*) patients.

Materials and Methods

Subjects

This study comprises individuals from two independent patient cohorts. The first one corresponds to the Mapping of Inflammatory Markers in Chronic Kidney Disease (*MIMICK*) cohort, the protocol of which has been described elsewhere in more detail.[10] This cohort includes prevalent patients (n=228) on maintenance HD therapy recruited during the period of October 2003 to September 2004 in six dialysis units in the Stockholm-Uppsala (Sweden) region. Patients were observed for a period of 3 months and inflammatory biomarkers were measured at the beginning and after 3 months, with subsequent follow-up for survival analyses. During the 3 months observational period, 3 patients died, 24 additional individuals had at least one missing value in one of the inflammatory markers studied. Therefore, 201 patients with complete data for all inflammatory markers at both time-points were included. From inclusion on forward, events of death were recorded, with no loss to follow-up. The Ethics Committee of Karolinska Institutet (Stockholm, Sweden) approved the protocol and informed consent was obtained from each patient. To replicate findings, a sample from the Netherlands Cooperative Study on the Adequacy of Dialysis (*NECOSAD*) study was included.[11] Briefly, NECOSAD is a prospective follow-up study including all incident dialysis patients from 38 dialysis centers in the Netherlands between 1997 and 2002. This study includes 472 patients with serum CRP assessed at 3 and 6 months after start of HD therapy. The NECOSAD protocol was approved by the Ethics committees of all participating centers and while being informed, all patients consented. In both cohorts, comorbidity was classified according to Davies et al.,[12] on a 7 point

scale which was later on simplified into 3 risk categories (low, medium and high comorbidity risk). Nutritional status was quantified by means of the subjective global assessment which, for reasons of simplicity, was trans-calculated to a 3 point scale.[13] Body mass index (*BMI*) was calculated as the body weight (kg) divided by the squared height (m^2).

Biochemical Methods

In both cohorts, venous blood was obtained before the dialysis session at each time point. Plasma was separated, and samples were kept frozen at -80 °C if not analyzed immediately. CRP in the NECOSAD was analyzed with an immunoturbidimetric assay with a detection limit of 3 mg/L. In the MIMICK cohort, high-sensitivity CRP levels were measured by an immunometric assay (detection limit 0.1 mg/L) on an Immulite Analyzer (Immulite, DPC, Siemens, California) similarly to plasma IL-6 and TNF- α levels (Immulite DPC, Siemens, California). Serum albumin levels were measured with bromecresol purple in the MIMICK cohort, whereas immunonephelometry was used in the NECOSAD.

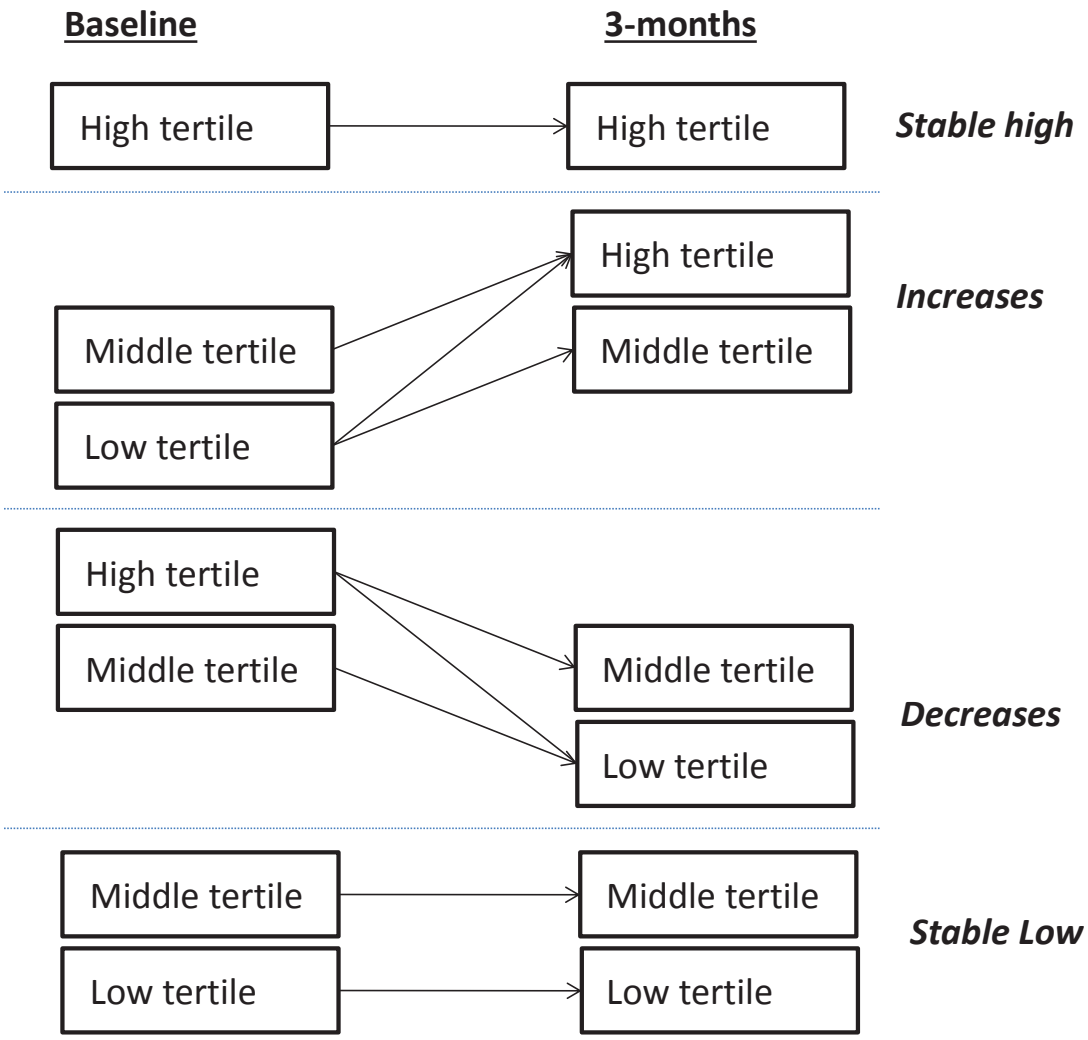
Statistical Methods

At each time point, patients were grouped according to each biomarker's tertiles of distribution (low, middle, high). The change in inflammatory marker was categorized according to the fluctuation between the tertiles of the studied biomarker at both time points (**Figure 1**). From the nine possible combinations, four groups were created by clustering patients with changes in the same direction: a) Individuals who showed a change to lower tertiles were classified as the "decrease" group; b) Individuals showing an increase to upper tertiles were assigned to the "increase" group; c) Individuals with both values within the highest tertile of distribution were labeled as "stable high" group; d) Individuals with both values within the lower or the middle tertile were labeled as "stable low" group. The same procedure was applied for each inflammatory mediator and for each cohort separately. Additionally, an extra categorization was performed for CRP values using the internationally accepted CRP thresholds (the CDC/AHA) of >3 mg/L and >10 mg/L.[14]

To test differences between the four groups, Kruskal Wallis, one-way ANOVA, and Chi square tests were applied for normally, non-normally distributed and categorical data, respectively. In the analysis of survival, Kaplan Meier curves were created and Cox proportional hazards model were used to calculate hazard ratios (*HR*). Since age, sex, comorbidities and nutritional status are known to interact with inflammation and influence mortality, they were included as confounders in multivariate Cox models. To take into account the potential confounding effect of baseline inflammatory levels, the logarithmic transformed value was included in crude as well as in multivariate analyses. Since NECOSAD is composed of incident patients with identical preceding time on dialysis, dialysis vintage was not included as covariate in the Cox models for this cohort. All variables satisfied the proportional hazards assumption. As sensitivity analyses, different cut-off values (p40 and p80) were used to form the different groupings. Also, in both cohorts, hazard ratios were recalculated using one cut-off value for CRP (10 mg/L) on both time points to define the different groupings.

To assess the correspondence between changes of the different inflammatory markers we used Pearson correlation tests. For all statistical tests, SPSS version 16.0 (SPSS Inc., Chicago, USA) was used. For all hazard ratios, a 95% confidence intervals (95%CI) not including 1 and for all other tests, a p-value smaller than 0.05, were considered to be statistically significant. Kaplan Meier figures were created using Prism 5.02 (Graphpad, 1992).

Figure 1. Classification of trimestral variation patterns for each inflammatory marker



Results

In the MIMICK cohort, the 33rd and 66th percentiles of CRP distribution were 3.6 and 14 mg/L for the first measurement and 3.6 and 12 mg/L for the second measurement, respectively. In the NECOSAD cohort, these values were 3.0 and 12.0 mg/L plus 4.0 and 12.0 mg/L for the two consecutive measurements correspondingly.

Table 1. Baseline characteristics of patients included in the study and after stratification according to CRP tertile variation categories in MIMICK subjects[1]

	All patients	Stable low[1]	Decrease[1]	Increase[1]	Stable high[1]	p-value
	n=201	n=82	n=40	n=42	n=37	
Baseline characteristics						
Men, %[4]	56.7	52.4	62.5	59.5	56.8	0.731
Age, years[5]	62.9 (14.2)	60.6 (15.4)	62.9 (14.3)	63.0 (15.0)	66.6 (11.5)	0.220
BMI, kg/m^2[,5]	24.5 (5.2)	24.2 (4.8)	24.4 (4.9)	24.4 (5.0)	25.2 (7.1)	0.842
Dialysis vintage, months[6]	28 (15 to 57)	29 (17 to 54)	29 (16 to 55)	19 (8 to 63)	34 (11 to 62)	0.287
Time dialysis per week, hours[6]	12.0 (12.0 to 13.5)	12.0 (12.0 to 13.5)	12.0 (12.0-13.5)	12.0 (12.0 to 13.5)	12.0 (10.9 to 12.50)	0.397
Low/medium/high Davies score, %[4]	20.4/56.2/23.4	31.7/48.8/19.5	15.0/57.5/27.5	7.1/69.0/23.8	16.2/56.8/27.0	0.048
Protein-energy wasting , %[3,4]	46.0	36.2	47.5	50.0	61.1	0.083
CRP at baseline, mg/L[6]	6.4 (2.6 to 18.5)	2.9 (1.2 to 6.0)	18.0 (6.5 to 31.3)	4.9 (2.5 to 8.1)	29.0 (22.0 to 47.5)	-
ΔCRP, mg/L[6]	-0.3 (-4.3 to 4.5)	-0.2 (-1.0 to 0.7)	-12.2 (-25.2 to -4.2)	9.9 (6.8 to 25.9)	-3.0 (-13.5 to 13.5)	-
IL-6 at baseline, pg/mL[6]	8.6 (5.1 to 15.0)	5.6 (3.5 to 8.9)	10.3 (7.3 to 15.8)	8.6 (5.1 to 12.7)	18.9 (11.0 to 26.9)	<0.0001
ΔIL-6, pg/mL[6]	0.2 (-2.2 to 2.8)	0.2 (-1.4 to 2.0)	-2.1 (-7.0 to 0.4)	4.90 (-0.1 to 12.0)	0.6 (-4.9 to 7.4)	<0.0001
TNF-α at baseline, pg/mL[6]	13.9 (11.1 to 16.8)	12.6 (10.6 to 15.3)	14.4 (11.3 to 16.9)	13.5 (10.9 to 15.9)	15.9 (13.8 to 18.3)	0.005
ΔTNF-α, pg/mL[6]	-0.2 (-1.9 to 1.7)	0.4 (-1.4 to 2.5)	-0.6 (-3.0 to 0.6)	-0.2 (-1.8 to 2.8)	-1.1 (-2.4 to1.3)	0.020
Characteristics during follow-up						
N. of deaths[4]	97	25	17	29	26	<0.0001
Time till death, months[6]	17.3 (8.4 to 28.1)	18.0 (10.6 to 30.8)	21.5 (8.3 to 31.7)	13.5 (8.3 to 23.0)	18.3 (6.6 to 28.9)	0.059

1. CRP variation groups were constructed according to changes in tertiles of the distribution at baseline and 3 months measurement (see methods).
2. Protein-energy wasting was defined as a SGA>1 (see methods).
3. ΔCRP was calculated by subtracting the level at zero months from the level at three months.
4. Differences between groups in categorical data were tested by means of a Chi square test.
5. Data are expressed as mean (SD). Differences between groups were tested by means of a one-way ANOVA test.
6. Data are expressed as median (IQR). Differences between groups were tested by means of a Kruskal-Wallis test.

Table 2. Baseline characteristics of patients included in the study and after stratification according to CRP tertile variation categories in NECOSAD subjects[1]

	All patients	Stable low[1]	Decrease[1]	Increase[1]	Stable high[1]	p-value
	n=472	n=179	n=115	n=95	n=83	
Baseline characteristics						
Men, %[4]	57.2	54.2	57.4	56.8	63.9	0.538
Age, years[5]	62.2 (13.8)	58.3 (14.8)	64.3 (13.3)	62.5 (13.2)	67.5 (10.2)	<0.0001
BMI, kg/m[2,5]	24.6 (4.2)	24.7 (3.8)	23.9 (3.9)	24.4 (3.5)	25.8 (6.0)	0.018
Time dialysis per week, hours[6]	9.0 (8.0 to 12.0)	9.0 (8.0 to 12.0)	9.0 (8.0 to 12.0)	9.0 (8.0 to 12.0)	9.0 (8.0 to 12.0)	0.552
Low/medium/high Davies score, %[4]	39.2/50.8/10.0	45.8/45.3/8.9	37.4/55.6/7.0	45.3/47.4/7.4	20.5/60.2/19.3	0.001
Protein-energy wasting , %[2,4]	29.9	24.5	37.0	23.2	46.8	0.002
CRP at baseline, mg/L[6]	6.0 (3.0 to 16.0)	3.0 (3.0 to 6.0)	15.0 (7.0 to 23.0)	3.0 (3.0 to 7.0)	24.0 (17.0 to 48.0)	-
ΔCRP, mg/L [3,6]	0.0 (-4.0 to 4.0)	0.0 (0.0 to 1.0)	-9.0 (-19.0 to -3.0)	9.0 (5.0 to 17.0)	1.0 (-14.0 to 18.0)	-
Characteristics during follow-up						
N. of deaths[4]	206	57	56	36	57	<0.0001
Time to death, months[6]	20.1 (8.6 to 32.7)	28.0 (15.5 to 39.8)	19.3 (5.3 to 32.3)	20.4 (7.7 to 39.4)	12.8 (5.4 to 23.1)	<0.0001

1. CRP variation groups were constructed according to changes in tertiles of the distribution at baseline and 3 months measurement (see methods).
2. Protein-energy wasting was defined as a SGA>1 (see methods).
3. ΔCRP was calculated by subtracting the level at zero months from the level at three months.
4. Differences between groups in categorical data were tested by means of a Chi square test.
5. Data are expressed as mean (SD). Differences between groups were tested by means of a one-way ANOVA test.
6. Data are expressed as median (IQR). Differences between groups were tested by means of a Kruskal-Wallis test.

Table 3. Crude and adjusted mortality risk for each variation category according to tertile categorization

	Groups, [1]	Crude, HR (95% CI)		Adjusted, HR (95% CI)[2]	
MIMICK cohort					
CRP	Stable low	1.00		1.00	
	Decrease	1.43	(0.77 to 2.65)	1.38	(0.73 to 2.60)
	Increase	3.27	(1.91 to 5.60)	3.13	(1.79 to 5.45)
	Stable high	2.98	(1.71 to 5.20)	2.79	(1.58 to 4.94)
IL-6	Stable low	1.00		1.00	
	Decrease	1.94	(1.02 to 3.68)	1.76	(0.92 to 3.38)
	Increase	3.38	(1.86 to 6.14)	3.62	(1.96 to 6.69)
	Stable high	5.73	(3.30 to 9.97)	3.80	(2.10 to 6.87)
TNF-α	Stable low	1.00		1.00	
	Decrease	1.27	(0.70 to 2.29)	1.43	(0.79 to 2.60)
	Increase	1.89	(1.09 to 3.25)	1.81	(1.04 to 3.14)
	Stable high	2.46	(1.49 to 4.07)	1.59	(0.92 to 2.74)
NECOSAD cohort					
CRP	Stable low	1.00		1.00	
	Decrease	1.68	(1.15 to 2.46)	1.45	(0.98 to 2.16)
	Increase	1.27	(0.83 to 1.94)	1.39	(0.91 to 2.15)
	Stable high	3.38	(2.31 to 4.94)	2.33	(1.58 to 3.45)

1. The stable-low group (see methods) served as the reference category.
2. After adjustment for age, sex, Davies Comorbidity score, protein-energy wasting (SGA>1), and log (vintage on dialysis).

Tables 1 and 2 depict the baseline characteristics of the patients included in this study according to the four CRP variation categories for the MIMICK and NECOSAD cohorts, respectively. Also, characteristics of follow-up are presented. In the MIMICK cohort, no difference was observed among the groups except for the severity of comorbidities and dialysis vintage: patients with increasing CRP levels having more frequently a comorbidity ≥ 2 (high comorbidity risk) and a lower dialysis vintage. In addition, baseline values and changes of IL-6 and TNF-α were also significantly different between all groups. In the NECOSAD cohort however, significant differences existed with regard to age, BMI, comorbidities and malnutrition across the four CRP variation groups: patients with elevated CRP levels on both time points were older, more often malnourished, had a higher BMI and more comorbidities.

In the MIMICK cohort, survival was assessed for each inflammatory biomarker after a median (IQR) follow-up of 38.4 (17.4-45.1) months, during which 97 (48.3%) individuals died. As shown in **Figure 1a-c**, a similar mortality pattern was observed for fluctuation categories of CRP, IL-6 and TNF-α. Crude and adjusted HRs are presented in **Table 3**. As compared with patients from the stable low group (reference), individuals who increased or had persistently elevated concentration of inflammatory biomarkers experienced an increased mortality risk, both crude and adjusted.

The magnitude of the HRs for these two categories was, from a clinical perspective, similar. For the case of IL-6, a decrease during the observational period was also associated with an increased mortality risk in the crude analysis (HR 1.94 [95% CI: 1.02-3.68]). Although adjustments made significance disappear, the magnitude of the HR was still substantial (1.76 [0.92-3.38]).

Table 4 illustrates a correlation matrix among the changes in inflammatory markers (deltas, as continuous variables) over the 3 months period. The correlation between ΔCRP and ΔIL-6 was substantial. On the other hand, correlations between ΔIL-6 and ΔTNF-α and between ΔCRP and ΔTNF-α, were relatively weak. In crude (3.38 [2.31-4.94]) and adjusted (2.33 [1.58-3.45]) Cox analysis (**Table 3**), patients within the stable high group exhibited the highest mortality hazard. Patients who showed decreases in CRP concentrations also presented an increased mortality risk in crude analysis (1.68 [1.15-2.46]), being barely lost after adjustment for confounders (1.45 [0.98-2.16]), and reaching a similar magnitude as the increase group.

As sensitivity analyses we used in both cohorts different cut-off values based on quartiles; however, results did not change (data not shown). Finally, **Table 5** repeats the analysis using the established CRP thresholds of 3 and 10 mg/L. Results confirm the same trend, namely that stable high levels associated with the highest mortality risk, followed by the increase group in the MIMICK cohort.

Table 4. Correlation matrix of changes in inflammatory markers

	ΔCRP	ΔIL-6
ΔIL-6	0.468**	-
ΔTNF-α	0.103	0.190*

Correlations were calculated by means of Pearson correlation tests; *p=0.05; ** p<0.001.

Discussion

The present study is the first to concurrently analyze the implications of CRP, IL-6 and TNF-α trimestral variation on outcome in HD patients. Our results show a similar survival pattern for all three biomarkers. Both an increase as well as a persistent elevation in all these biomarkers was linked to a poor prognosis during the follow-up period. The concordance between the changes of these biomarkers was low, especially between ΔCRP and ΔIL-6 with ΔTNF-α.

Our finding of an increased mortality risk amongst individuals with persistently elevated serum CRP levels is in agreement with previous studies in HD patients, which substantially differed regarding lengths and frequency of CRP measurement.[6,7,15] Also, our observations accord with findings from a cross-sectional study in which measures of cardiac hypertrophy were more prevalent amongst HD patients with persistently elevated CRP levels.[16] A novel finding in our study is that increasing levels of CRP over the 3 months period in prevalent patients are also associated with a higher mortality risk in both uni- and multi-variate analysis, agreeing with a small report in patients on continuous peritoneal dialysis.[8]

Table 5. Crude and adjusted mortality risk for each variation category according to the established CRP thresholds of 3 and 10 mg/L

	Groups[1]	Crude	Adjusted
		HR (95%CI)	HR (95%CI)[2]
MIMICK cohort			
CRP	Stable low	1.00	1.00
	Decrease	1.30 (0.67 to 2.52)	1.33 (0.67 to 2.62)
	Increase	3.25 (1.84 to 5.73)	2.77 (1.55 to 4.93)
	Stable high	2.92 (1.69 to 5.07)	2.36 (1.34 to 4.16)
NECOSAD cohort			
CRP	Stable low	1.00	1.00
	Decrease	1.39 (0.92 to 2.11)	1.16 (0.76 to 1.79)
	Increase	1.35 (0.89 to 2.05)	1.28 (0.84 to 1.96)
	Stable high	2.62 (1.81 to 3.81)	1.86 (1.27 to 2.72)

1. The stable-low group (see methods) served as the reference category.
2. Adjusted for age, sex, Davies score, protein-energy wasting (SGA>1), and log (vintage on dialysis).

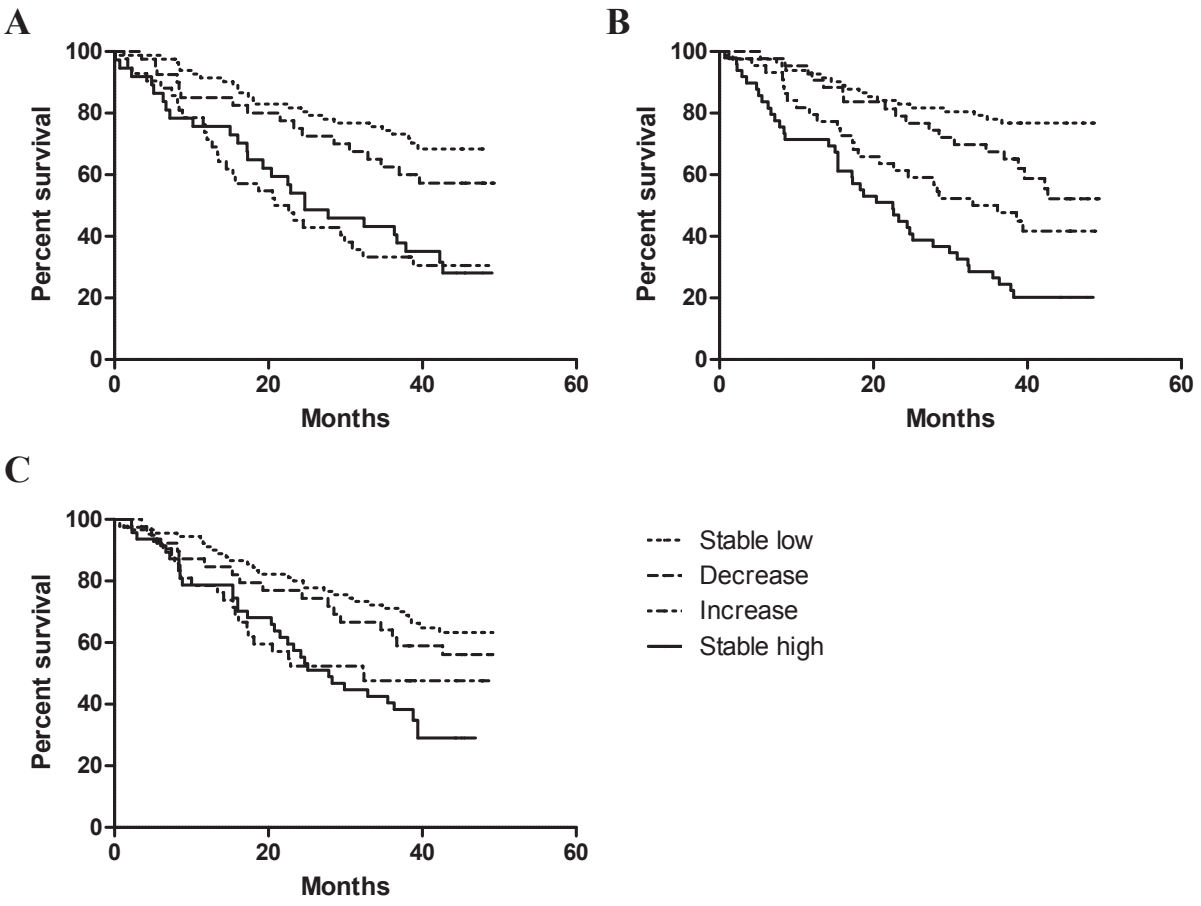


Figure 2. Kaplan-Meier survival curves in MIMICK patients according to CRP (Panel A), IL-6 (Panel B) and TNF-α (Panel C) variation groups.

Results were partially replicated in a second cohort of incident patients, in whom both increases and decreases of CRP were similar in magnitude in adjusted analyses. The inclusion of incident or prevalent patients in each of these cohorts, together with different baseline characteristics, may have influenced at this level.

Our analysis also longitudinally assesses the implications of IL-6 or TNF-α variation on HD outcome. We found a similar relation between mortality and variation patterns for all three biomarkers, thereby complementing the reported associations between single measurements of these markers and mortality.[3,17] In this context, it must also be noted that the association between inflammatory marker variability and mortality was the strongest for IL-6. A finding which is in line with previous observations with single measurements.[3,18] While the cross-sectional correlations between single measurements of TNF-α, CRP and IL-6 are consistently reported to be strong.[19,20] and a congruent pattern of altered cytokine profiling is observed cross-sectionally in HD patients,[21] we anticipated a better correlation between the three month variation patterns of these inflammatory markers.

Several differences should be acknowledged as limitations. Firstly, the cohorts share different incident (NECOSAD) and prevalent (MIMICK) designs. Secondly, while in the MIMICK CRP was measured with a high-sensitivity assay, a non-high-sensitivity assay with a detection limit of 3 mg/L was used in the NECOSAD. Nonetheless, sensitivity analyses using other cut-offs did not alter our findings, and we could recently demonstrate an excellent agreement between high-sensitivity and non high-sensitivity CRP measurements on mortality prediction in this same patient material.[25] A final drawback is that this study was performed in patients treated with HD, who may be different from patients treated with other dialysis modalities. This would limit the generalizability of our findings to other populations.

Altogether, our study indicates that persistent elevation and increases of CRP, IL-6, and TNF-α over a short period of time associate with a worse outcome. Since the correlation between these changes was not strong, it is likely that different inflammatory pathways are in parallel influencing the CKD patient´s risk. Whilst our findings may be of help to physicians when interpreting the evolution of the inflammatory response in HD patients, the question whether reduction of inflammation or stabilization of its variability could translate into improved survival remains, however, unanswered.

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