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RESEARCH ARTICLE

Cystatin C, NT-proBNP, and inflammatory markers in acute heart failure: insights into the cardiorenal syndrome

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Abstract

Background: Inflammation is thought to be a mediator in the pathophysiology of the cardiorenal syndrome. We evaluated the interactions between kidney function, cardiac stress, and various inflammatory cytokines in patients with acute heart failure (AHF). The effect on 1-year mortality was also assessed.

Methods and results: Plasma levels of cystatin C, NT-proBNP, and inflammatory cytokines (interleukin [IL]-6, tumor necrosis factor-α [TNF-α], IL-10) were measured in consecutive patients ($n = 465$) hospitalized for AHF. After adjustment for demographic characteristics and comorbidities, TNF-α had the strongest relation with renal function ($\beta = 0.39$, $P < 0.0001$). Elevated TNF-α levels were seen in patients with high cystatin C, irrespective of NT-proBNP. Levels of IL-6 ($\beta = 0.26$, $P < 0.0001$) and IL-10 ($\beta = 0.15$, $P < 0.01$), but not TNF-α, were associated with NT-proBNP. Moreover, the most elevated levels of IL-6 were seen in patients with combined high NT-proBNP and high cystatin C. Cox regression analysis found IL-6 above median to be independently predictive of mortality (hazard ratio 1.9; 95% CI 1.2–2.9, $P = 0.003$). TNF-α was not significantly associated with prognosis in the overall population after adjustment for multiple covariates, but improved risk stratification in the subgroup with low cystatin C and NT-proBNP.

Conclusion: Levels of TNF-α in AHF are related to kidney function, but not to NT-proBNP. IL-6 seems to be more associated with cardiac stress. Patients with severe dual organ dysfunction have the highest levels of IL-6 and TNF-α. Different relations of inflammatory cytokines to renal function and cardiac stress need to be considered when evaluating heart–kidney interactions.

Keywords: Cardiovascular disease, growth factors/cytokines/inflammatory mediators, renal disease

Introduction

The pathophysiological interaction between the heart and the kidney, also called the cardiorenal syndrome (CRS), has risen into focus because of its detrimental effect on prognosis. Impaired renal function is common in heart failure and associated with unfavorable outcomes (Siirilä-Waris et al. 2006, Smith et al. 2006,

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Heywood et al. 2007). Conversely, chronic kidney disease (CKD) is independently associated with increased cardiovascular morbidity and mortality (Sarnak et al. 2003, Go et al. 2004). This is in part due to higher prevalence of cardiovascular risk factors, but also higher prevalence and severity of concomitant cardiovascular diseases in patients with renal insufficiency. In the CRS, heart failure leads to kidney dysfunction and/or vice versa through numerous pathways of interaction between the heart and kidney. Inflammation is thought to be one of the mechanisms mediating this interaction (Ronco et al. 2008, 2010).

Elevated levels of tumor necrosis factor-α (TNF-α) found in chronic heart failure patients have been associated with increased morbidity and mortality (Aukrust et al. 1999, Rauchhaus et al. 2000, Dunlay et al. 2008). In acute heart failure (AHF), higher circulating levels of inflammatory cytokines (e.g. interleukin [IL]-6 and TNF-α) have been described (Suzuki et al. 2005, Chen et al. 2008). However, inflammatory markers are also elevated in CKD (Shlipak et al. 2003, Stenvinkel et al. 2005) and inflammation has been shown to predict adverse cardiovascular outcome in patients with end-stage renal disease (Roberts et al. 2006). Little is known about levels and effects of inflammatory cytokines in patients with heart failure and varying degrees of renal dysfunction, that is, the CRS.

The purpose of this study was to test the hypothesis that levels of inflammatory cytokines relate to renal function in AHF. We measured proinflammatory markers such as IL-6 and TNF-α as well as the anti-inflammatory cytokine IL-10 in patients hospitalized for AHF. We evaluated their association with cystatin C, a sensitive measure of renal function, and NT-proBNP, as a marker of cardiac stress. The impact of the inflammatory cytokines on mortality was also assessed.

Methods

FINN-AKVA is a prospective, observational, multicenter study on AHF (Siirilä-Waris et al. 2006). Consecutive patients presenting with symptoms, signs, and diagnostic findings of AHF and requiring hospitalization were enrolled at 14 participating centers (local, central, and university hospitals) during 3 months in 2004. The patients were systematically characterized and clinical data on admission recorded in detail. The diagnosis of AHF had to be confirmed during hospital stay, using the criteria of the ESC guidelines (Nieminen et al. 2005). Centralized analyses of cystatin C, creatinine, IL-6, IL-10, TNF-α, and NT-proBNP were performed from blood samples taken ~48-h post-admission. Hemoglobin and sodium were measured as routine admission samples locally at each center. Of the 620 patients enrolled in the study, 574 were hospitalized at centers participating in biomarker blood sampling. Patients dead ($n=6$) or discharged ($n=16$) prior to blood sampling and patients with missing values for one or several cytokines ($n=87$) were excluded from this analysis. The present study includes 465 patients with measurements of cystatin C, NT-proBNP, and the studied inflammatory cytokines. Written informed consent was obtained from all patients. The national ethics committee approved our multicenter study.

Cystatin C was measured using the Dako Cytomation immunoturbidimetric assay, and cystatin C values below the upper limit of the reference interval recommended by the manufacturer (cystatin C <1.2 mg/L in adults ≤50 years of age and <1.4 mg/L for people aged over 50 years) were considered normal renal function. Plasma concentrations of IL-6, TNF-α, and IL-10 were assayed using commercial enzyme-linked immunosorbent assay (ELISA) systems (Quantikine kit; R&D Systems Inc.). The lower limits of detection of the IL-6, TNF-α, and IL-10 assays were 0.70, 0.12, and 0.50 ng/L plasma, respectively. Plasma creatinine and NT-proBNP (Roche Diagnostics) were analyzed using commercially available kits. The four-variable MDRD equation was used to estimate glomerular filtration rate (eGFR) from measured creatinine values (Levey et al. 2006).

Relationships between cystatin C, NT-proBNP, and each of the inflammatory markers were evaluated by drawing correlation plots and calculating Pearson's correlation coefficients. As the observed distributions of the studied biomarkers were skewed to the right, logarithmically transformed values were used in these analyses. The relation was further assessed using linear regression and standardized regression coefficients (β), adjusting for possible confounders such as age, gender, medical history (coronary artery disease [CAD], previous heart failure, hypertension, diabetes, cerebrovascular disease), current smoking, medication on admission (β-blocker, angiotensin-converting enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB], lipid-lowering therapy), New York Heart Association (NYHA) functional class on admission, as well as the presence of acute coronary syndrome (ACS) or clinical infection. Acute changes in renal function were evaluated in patients ($n=278$) with creatinine and cystatin C values measured on admission as well. Differences between admission and 48-h values were calculated. Acute kidney injury was defined either as a rise in creatinine by 0.3 mg/dL (AKI_{Crea}) (Mehta et al. 2007) or a rise in cystatin C by 0.3 mg/L (AKI_{CysC}) (Lassus et al. 2010). Linear regression was also used to analyze whether the change in renal function from admission to 48 h was a significant predictor of the levels of inflammatory markers.

Levels of inflammatory cytokines were assessed in relation to renal function (i.e. cystatin C) and cardiac stress (i.e. NT-proBNP). For this purpose, levels of cystatin C, NT-proBNP, and markers of inflammation were assessed in quartiles of eGFR. Furthermore, patients were stratified according to cystatin C and NT-proBNP medians and levels of the inflammatory cytokines were assessed in these groups. This resulted in four categories: (I) a group with cystatin C levels below median and NT-proBNP below median ($CysC_{low/}NT\text{-}proBNP_{low}$), (II) a group with

cystatin C levels below median and NT-proBNP above median ($CysC_{low/}NT\text{-}proBNP_{high}$), (III) a group with cystatin C levels above median and NT-proBNP below median ($CysC_{high/}NT\text{-}proBNP_{low}$), and finally (IV) patients with both cystatin C levels and NT-proBNP above median ($CysC_{high/}NT\text{-}proBNP_{high}$). Differences in demographic, clinical, and laboratory parameters between groups were examined by using the Kruskall–Wallis and Mann–Whitney *U*-tests as appropriate.

Vital status (all-cause mortality) at 12 months and time of death were obtained for all patients from the national Population Register Centre, which includes data on all deaths in Finland. Receiver operating characteristics (ROC) analysis was used to assess the ability of the inflammatory cytokines to predict mortality. Kaplan–Meier survival curves were plotted for the inflammatory markers (above and below median) and differences between strata were evaluated by the log rank test. Cox regression analysis was used to calculate hazard ratios (HR) of 1-year mortality (including in-hospital deaths) for the inflammatory biomarkers. Adjustment was made for age, gender, medical history (hypertension, CAD, previous heart failure, cerebrovascular disease, diabetes), clinical presentation (NYHA class, systolic and diastolic blood pressure, ACS on admission), cystatin C, and NT-proBNP in the multivariable models. The proportional hazards assumption was tested using partial residuals plots and satisfied for all the studied biomarkers. HR are shown with 95% confidence intervals (CI) and $P<0.05$ was regarded statistically significant. SPSS statistical software (version 15.0.1) was used for statistical analyses.

Results

Study population

Baseline characteristics of the study population are shown in Table 1. Patients were elderly, and half of them were female. Left ventricular ejection fraction was preserved (LVEF ≥45%) in 52% of patients. The characteristics of patients classified in different cystatin C/NT-proBNP strata are depicted in Table 1. Measured biomarker levels are summarized in Table 2. Overall, 201 patients had eGFR<60 mL/min, whereas 199 patients (43%) had elevated cystatin C levels.

Inflammatory cytokines and correlations

Correlations of (log)cystatin C and (log)NT-proBNP with the logarithm of the inflammatory markers are shown in Figure 1 and results of the linear regression in Table 3. Cystatin C was found to correlate most strongly with TNF-α ($R=0.47$, $P<0.0001$), whereas the correlation with IL-6 was weaker ($R=0.17$, $P=0.0003$) (Figure 1). These associations were confirmed and remained highly significant in the linear regression analysis adjusting for possible confounders (Table 3). However, adjusting NT-proBNP markedly attenuated the relationship between cystatin C and IL-6.

NT-proBNP showed different and more moderate associations with the inflammatory cytokines. After adjustment for demographics and comorbidities, there was a relation between NT-proBNP and IL-6 ($\beta=0.26$, $P<0.001$), but not between NT-proBNP and TNF-α. Actually, adjustment for cystatin C alone eliminated all associations between NT-proBNP and TNF-α (Table 3). IL-10 correlated only weakly with NT-proBNP. Cystatin C was also a predictor of NT-proBNP levels after adjustment ($\beta=0.26$, $P<0.0001$). The studied inflammatory cytokines were significantly intercorrelated (data not shown). Levels of all inflammatory markers were higher in patients with acute kidney injury ($P<0.01$ for all three markers with both AKI_{CysC} and AKI_{Crea}), but the change in renal function was not related to levels of inflammatory markers at 48 h ($\beta < 0.1$ and $P>0.1$ for change in cystatin C and each of the three cytokines).

There was an increase in cystatin C, NT-proBNP, and TNF-α by quartile of eGFR (Figure 2). Median levels of IL-6 were similar in the three upper quartiles of eGFR, with higher levels seen only in the lowest quartile (20.2 ng/L in Q4 [eGFR <48 mL/min] vs. 14.4 ng/L in Q1 [eGFR >81 mL/min), $P=0.2$ by Kruskall–Wallis test across all quartiles). Levels of IL-6 and TNF-α differed between strata of cystatin C and NT-proBNP, whereas levels of the anti-inflammatory cytokine IL-10 showed no significant change between groups (Table 2). Specifically, TNF-α levels were significantly elevated in groups with high cystatin C, whereas NT-proBNP stratum had little effect on levels of TNF-α. In contrast, IL-6 levels were higher in the strata with high NT-proBNP. In particular, patients with both cystatin C and NT-proBNP above median had average IL-6 levels twice as high compared with patients with both markers below median.

Mortality analysis

During 12 months follow-up, 120 patients (26%) died. The proinflammatory cytokines had comparable capability to discriminate between patients who died and survivors with an area under the curve (AUC) of 0.64 for IL-6 and 0.66 for TNF-α ($P<0.001$ for both). IL-10 had weaker predictive properties (AUC 0.56, $P=0.06$) and the effect on mortality was not further analyzed. In the Kaplan–Meier analysis, both high IL-6 (mortality 17% vs. 34% for IL-6 below and above median, respectively, $P<0.001$) and high TNF-α (18% vs. 34%, $P<0.001$) were associated with increased mortality and provided similar risk stratification (Figure 3). However, although high IL-6 was independently associated with mortality at 12 months (adjusted HR 1.9 [95% CI 1.2–2.9], $P=0.003$) in the proportional hazards model, high TNF-α was not an independent predictor of death (HR 1.1; 95% CI 0.7–1.7, $P=0.7$) in the total study population.

Additional analyses were performed in cystatin C/NT-proBNP strata to explore and better understand the effect of the cytokines on mortality. IL-6 above median was associated with worse survival, but mainly in the

Table 1. Patient characteristics of the study population and in cystatin C/NT-proBNP strata.

Characteristics	All ($n=465$)	$CysC_{low}$/NT-BNP_{low}	$CysC_{low}$/NT-BNP_{high}	$CysC_{high}$/NT-BNP_{low}	$CysC_{high}$/NT-BNP_{high}	*P*-value
Age, years	74.8 (10)	69.8 (10)	75.9 (11)	76.4 (9)	78.0 (9)	<0.001
Female gender	225 (49)	58 (41)	46 (55)	50 (58)	71 (48)	0.05
History of						
Previous heart failure	242 (52)	56 (39)	36 (43)	54 (62)	95 (65)	<0.001
Coronary artery disease	260 (56)	57 (40)	38 (46)	58 (67)	105 (71)	<0.001
Myocardial infarction	127 (27)	23 (16)	24 (29)	28 (32)	51 (35)	0.003
Hypertension	264 (57)	79 (55)	40 (48)	56 (64)	88(60)	0.16
Diabetes	153 (33)	49 (34)	19 (23)	33 (38)	50 (34)	0.18
Chronic atrial fibrillation	131 (28)	32 (22)	17 (21)	32 (37)	49 (33)	0.02
Cerebrovascular disease	79 (17)	26(18)	10 (12)	16 (18)	26(18)	0.6
Chronic kidney disease	38 (8)	0 (0)	1 (1)	14 (16)	23 (16)	<0.001
Current smoker	53 (11)	21 (15)	13 (16)	5(6)	14 (10)	0.10
ACS on admission	139 (30)	40 (28)	29 (35)	18 (21)	51 (35)	0.10
Clinical infection	110 (24)	24 (17)	24 (29)	19 (22)	42 (29)	0.07
Medication on admission						
Beta blocker	294 (63)	81 (57)	44 (53)	60 (69)	108 (74)	0.003
ACEI/ARB	244 (53)	75 (52)	37 (45)	53 (61)	78 (53)	0.2
Lipid-lowering therapy	137 (30)	40 (28)	18 (22)	33 (38)	46 (31)	0.13
Heart rate, beats/min	92 (28)	91 (28)	102 (30)	88 (26)	88 (25)	0.004
Systolic BP, mmHg	148 (33)	149 (28)	141 (27)	157 (34)	144 (37)	0.003
Diastolic BP, mmHg	83 (20)	86 (20)	84 (19)	82 (20)	80 (20)	0.05
LVEF% ($n=317$)	45 (16)	47 (16)	41 (16)	51 (15)	42 (16)	<0.001
Hemoglobin, g/L	128 (18)	136 (17)	130(17)	122 (16)	122 (18)	<0.001
Sodium, mmol/L	138 (5)	139 (4)	138 (6)	139 (5)	138 (5)	0.04
Medication at discharge						
Beta blocker	378 (86)	120 (86)	73 (91)	68 (81)	113 (86)	0.3
ACEI/ARB	340 (77)	115 (82)	64 (80)	65 (77)	91 (69)	0.06
Mortality at 12 months	120 (25.8)	11 (7.7)	14 (16.9)	25 (28.7)	68 (46.3)	<0.001

Results are shown as numbers and percentages (%) or means and standard deviations (SD). *P*-value for Kruskall–Wallis test across groups. Medication at discharge for 441 patients discharged alive out of hospital. ACS = acute coronary syndrome, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, NYHA = New York Heart Association, BP = blood pressure, LVEF = left ventricular ejection fraction.

Table 2. Levels of the studied biomarkers in the study population and in cystatin C/NT-proBNP strata.

		Strata			
Characteristics	All ($n=465$)	$CysC_{low}$/NT-BNP_{low}	$CysC_{low}$/NT-BNP_{high}	$CysC_{high}$/NT-BNP_{low}	$CysC_{high}$/NT-BNP_{high}
Cystatin C, mg/L	1.30 (1.04–1.71)	1.02 (0.88–1.16)	1.07 (0.90–1.21)	1.67 (1.43–1.98)**,††	1.74**,†† (1.49–2.18)
Creatinine, μmol/L	88 (72–114)	0.84 (0.70–0.98)	0.89 (0.71–1.03)	1.23 (0.96–1.46)**,††	1.29**,†† (1.04–1.79)
eGFR, mL/min	64 (81–48)	81 (95–69)	75 (90–62)	52**,†† (64–40)	49**,†† (60–35)
IL-6, ng/L	15.2 (7.2–32.5)	11.3 (5.9–21.9)	16.2* (7.6–29.9)	12.6 (6.6–24.6)	23.6**,‡,† (10.1–47.4)
TNF-α, ng/L	1.5 (1.0–2.1)	1.1 (0.9–1.6)	1.1 (0.8–1.5)	1.7**,†† (1.4–2.3)	2.0**,†† (1.5–2.5)
IL-10, ng/L	1.8 (0.5–3.7)	1.7 (0.5–3.3)	2.1 (0.5–4.1)	1.6 (0.5–3.5)	2.1 (0.9–4.3)
NT-proBNP, ng/L	3951 (1987–8723)	1931 (736–2740)	8275** (5180–12501)	2331* (1280–3238)	9442**,†,‡ (5821–20242)

Results are shown as median with interquartile range (25th percentile–75th percentile). CysC low/high = CysC below/above median of 1.30 mg/L, NT-proBNP low/high = NT-proBNP below/above median of 3951 pg/L. $^{*}P<0.05$ vs. (I), $^{**}P<0.01$ vs. (I), $^{\dagger}P<0.05$ vs. (II), $^{\dagger\dagger}P<0.01$ vs. (II), $^{\ddagger}P<0.01$ vs. (III). Pairwise differences between groups assessed by Mann–Whitney *U*-test.

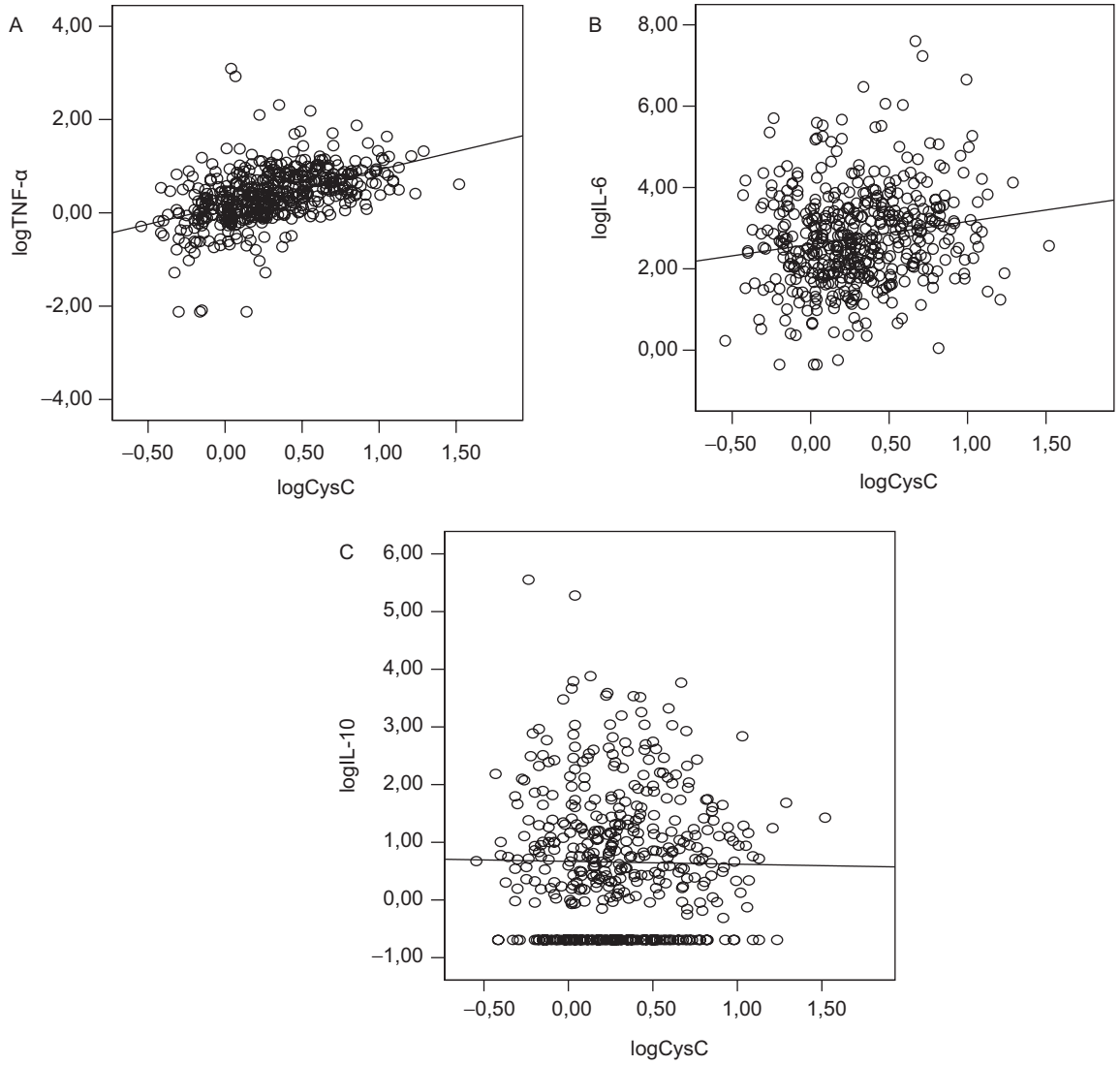

Figure 1. Correlation between cystatin C and (A) TNF-α, (B) IL-6, (C) IL-10. Correlation plots between the logarithm of the inflammatory cytokines and the logarithm of cystatin C. Pearson's correlation coefficients were: $R = 0.47$ ($P < 0.001$) for TNF-α, $R = 0.17$ ($P < 0.001$) for IL-6 and $R = -0.02$ ($P = 0.8$) for IL-10.

Table 3. Results of linear regression of cytokines with (log)cystatin C and (log)NT-proBNP.

		(log)IL-6		(log)TNF-α		(log)IL-10	
		β	*P*-value	β	*P*-value	β	*P*-value
(log)Cystatin C	Unadjusted	0.17	<0.001	0.47	<0.001	–0.02	0.8
	Adjusted†	0.09	0.05	0.42	<0.001	–0.05	0.2
	Adjusted*	0.18	<0.001	0.37	<0.001	0.01	0.8
(log)NT-proBNP	Unadjusted	0.26	<0.001	0.16	<0.001	0.12	<0.01
	Adjusted†	0.21	<0.001	–0.01	0.8	0.12	<0.01
	Adjusted*	0.26	<0.001	0.08	0.1	0.15	<0.01

IL-6 = interleukin 6, IL-10 = interleukin 10, TNF-α= tumor necrosis factor-α, NT-proBNP = N-terminal pro-brain natriuretic peptide.
†Adjusted for NT-proBNP or cystatin C alone.
*Adjusted for age, gender, history of previous heart failure, coronary artery disease, cerebrovascular disease, hypertension, diabetes, smoking status, medication at baseline (β-blocker, ACEI/ARB, lipid-lowering therapy), NYHA class, presence of acute coronary syndrome on admission, and clinical infection during hospitalization.

strata with an intermediate overall mortality, having either high cystatin C or high NT-proBNP (Figure 4). TNF-α did not improve risk stratification in patients having renal dysfunction. In contrast, TNF-α below median was associated with lower mortality (3% vs. 13%, $P = 0.03$) in the subgroup having a good prognosis overall (patients with low cystatin C and low NT-proBNP). The median of 1.1 ng/L was found to be of excellent negative predictive value (97%) in this subgroup, and thus could be of aid in risk assessment.

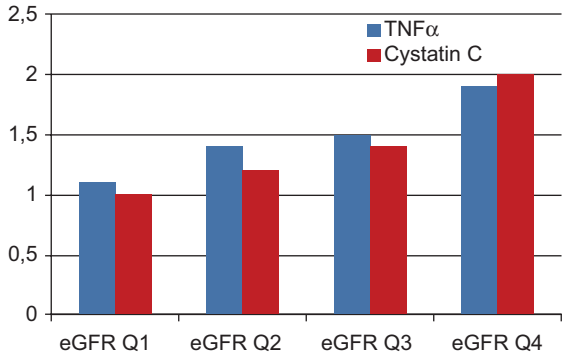

Figure 2. Levels of TNF-α and cystatin C by quartiles of eGFR. There was a stepwise increase in TNF-α and cystatin C levels for each quartile of eGFR. Kruskall–Wallis *P*-value <0.001 for both. Q1 = eGFR>81 mL/min, Q2 = eGFR 64–81 mL/min, Q3 = eGFR 48–64 mL/min, and Q4 = eGFR <48 mL/min.

Discussion

This study investigates the association between inflammation and the CRS by relating levels of inflammatory cytokines to markers of renal function and cardiac stress in a cohort of well-characterized patients with AHF. The main finding is the strong relationship between levels of the proinflammatory cytokine TNF-α and renal function. In fact, TNF-α correlates significantly with cystatin C, whereas no association was observed with NT-proBNP after adjustment for confounders. Although the markers of inflammations had only moderate discriminative capability on ROC analysis, IL-6 above median was an independent predictor of mortality. TNF-α could be used for risk stratification in patients with low cystatin C and low NT-proBNP.

The CRS has received much interest in recent years, and inflammation is thought to be one of the mechanisms potentiating the heart–kidney interaction (Ronco et al. 2008, 2010). Increased levels of inflammatory markers have been described in both acute and chronic heart failure (Lommi et al. 1997, Rauchhaus et al. 2000, Anker and Haehling 2004, Suzuki et al. 2005, Chen et al. 2008). TNF-α and IL-6 are among the most studied cytokines in heart failure, and levels have been found to be elevated in heart failure and to correlate with disease severity and prognosis (Hilfiker-Kleiner et al. 2006, Bozkurt et al. 2010) Nevertheless, there are also studies showing that levels of TNF-α are not related to hemodynamic indices or severity of heart failure (Lommi et al. 1997, Petretta et al. 2000, Suzuki et al. 2005). Indeed, TNF-α was not related to NT-proBNP in our study.

In this study, levels of TNF-α had the strongest association with cystatin C. In fact, a number of studies have found an inverse relationship between renal function and levels of TNF-α in CKD (Descamps-Latscha et al. 1995, Bolton et al. 2001, Cachofeiro et al. 2008). A previous study also showed similar correlation between TNF-α and cystatin C in elderly patients without CKD and eGFR ≥60 mL/min (Keller et al. 2007). The authors suggested that diminished

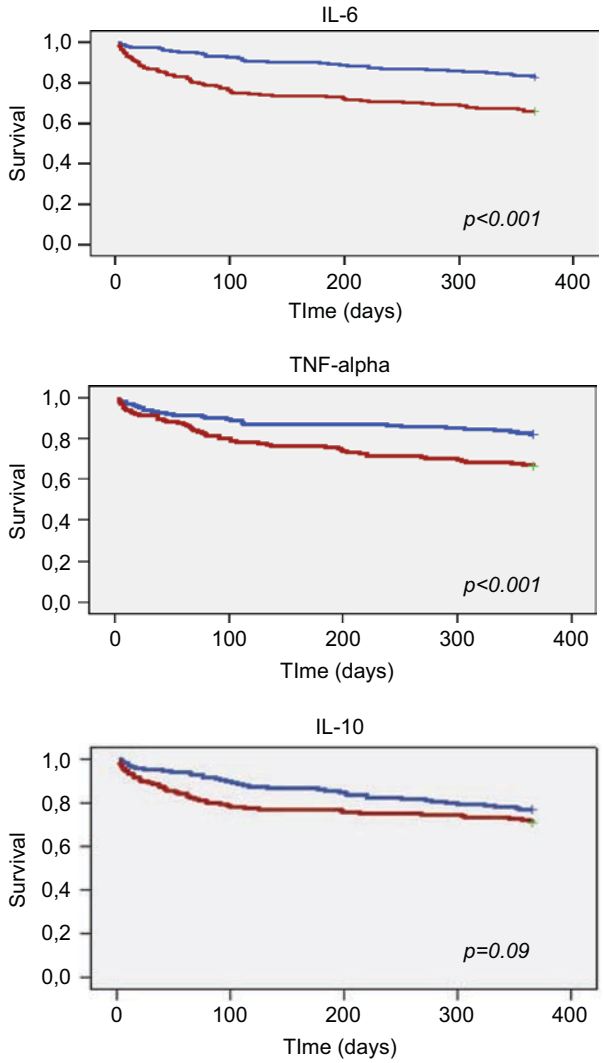

Figure 3. Survival curves for inflammatory cytokines in acute heart failure. Kaplan–Meier survival curves for patients with levels of IL-6, TNF-α, and IL-10 above (lower line) and below (upper line) the median. The mortality was significantly different for IL-6 and TNF-α.

renal clearance of TNF-α could be responsible for the higher levels observed in renal insufficiency, but the exact mechanism remains largely unknown. Thus, there is also an undisputable link between renal insufficiency and inflammation (Stenvinkel et al. 2005, Roberts et al. 2006).

Taken together, these data would suggest that elevated levels of TNF-α in patients with AHF might actually be a reflection of concomitant renal dysfunction and that even mildly impaired kidney function is associated with increasing TNF-α levels. Simply adjusting for cystatin C abolished the association between TNF-α and NT-proBNP. In contrast, the relation between TNF-α and cystatin C was not affected by NT-proBNP, and multiple adjustments did not attenuate the association. Previous studies on inflammatory markers in AHF have been of limited size and the cardiorenal axis often overlooked (Chen et al. 2008). One recent study in patients with chronic heart failure showed that TNF-α levels increased with declining renal function (Dunlay et al. 2008).

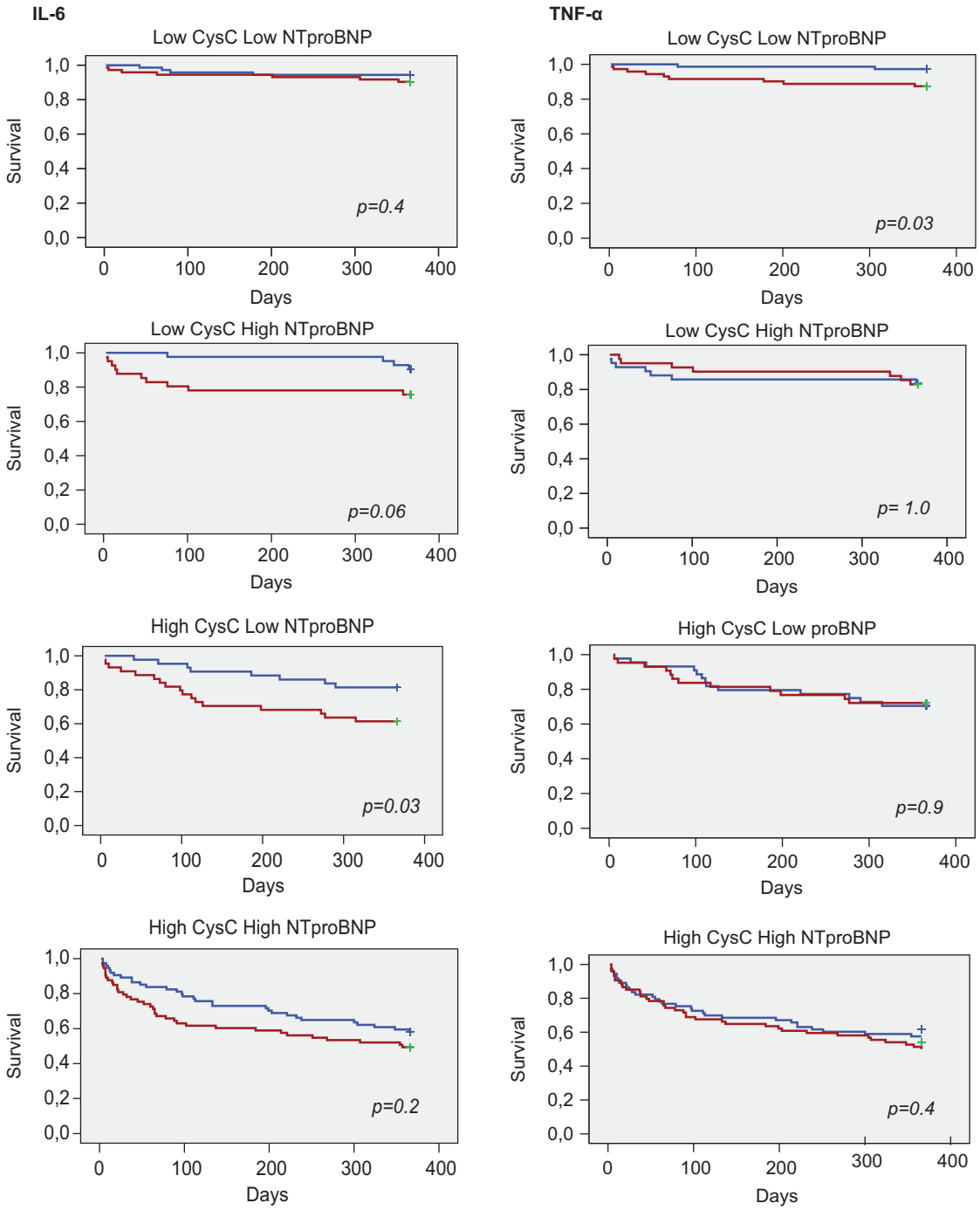

Figure 4. Kaplan–Meier curves by IL-6 and TNF-α median in CysC/NT-proBNP strata. Patients were divided in strata of cystatin C and NT-proBNP above (high) and below (low) median. The figure shows Kaplan–Meier curves for survival according to strata-specific median of IL-6 (left) and TNF-α (right). Please refer to Table 2 for median levels of biomarkers.

In the current study, IL-6 was the cytokine with the best correlation to NT-proBNP, a marker of cardiac stress and severity of heart failure. This is in line with previous observations that IL-6, but not TNF-α, correlated with the size of myocardial infarction and hemodynamic parameters in acute and chronic heart failure (Lommi et al. 1997, Puhakka et al. 2003, Suzuki et al. 2005). Still, IL-6 was related to cystatin C as well. IL-6 levels were higher only in the lowest eGFR quartile. Patients with worse renal function most likely also have more extensive and severe cardiac disease. Even if adjustment was made for available parameters residual confounding might explain the weaker, but significant, correlation between IL-6 and renal function. Other mechanisms, like direct stimulation of IL-6 production by TNF-α and many more uremia-related factors, can also be considered (Stenvinkel et al. 2005). IL-10 was also correlated with NT-proBNP, but the association was not strong. Unexpectedly, IL-10 levels had no relationship with cystatin C. IL-10 is cleared by the kidneys and elevated levels have been described in

renal insufficiency. Finally, patient stratification by the medians of cystatin C and NT-proBNP showed that levels of IL-6 increased in the group with NT-proBNP above median, but the highest levels were found in patients with high levels of both markers of organ dysfunction. In contrast, TNF-α were higher in patients with impaired renal function irrespective of NT-proBNP.

As already mentioned, inflammatory markers have previously been found to be predictive of outcome in chronic heart failure (Rauchhaus et al. 2000, Dunlay et al. 2008, Parissis et al. 2009). In this cohort of AHF patients, ROC analysis found only moderate ability for the inflammatory cytokines to discriminate mortality in AHF. Nevertheless, IL-6 was a predictor of mortality after adjustment for several other variables. The effect of the inflammatory cytokines seemed to be limited to patients with low–intermediate mortality risk. Patients with severe organ dysfunction, that is, the CRS, have a very high mortality rate and inflammation did not impact on prognosis in this group. The results of this study suggests that IL-6 and TNF-α might be useful for risk stratification in patients with less advanced disease and preserved renal function.

Limitations

This study is cross-sectional and does not determine causality between inflammation, renal function, and heart failure. In assessing renal function, the gold standard of a direct measurement of glomerular filteration rate (GFR) was not available. AHF is a dynamic process very different from the more stable phase of chronic heart failure, and both cytokine levels and renal function are subject to changes over time. Absolute levels of individual cytokines should be interpreted with caution. In addition, the cytokine network is very complex, and actual pathophysiological effects are difficult to assess. Factors not measured in this study, such as soluble TNF receptors, are known to alter the clinical response to individual cytokines.

Conclusions

The results of this study suggest that levels of TNF-α are strongly related to kidney function in patients hospitalized for AHF. Inflammatory cytokines play a role in the heart–kidney interaction, but their individual association to renal function and markers of cardiac stress merit further consideration when evaluating inflammation as part of the CRS. The findings indicate that markers of inflammation also carry prognostic information in AHF, but mainly in patients without severe cardiac and kidney dysfunction.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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