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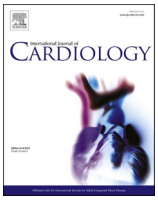

Short communication

Clinical characteristics and prognosis of patients with heart failure and high concentrations of interleukin-17D

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ABSTRACT

Aims: Heart failure (HF) is associated with cytokine activation and inflammation. Experimental evidence suggests that plasma interleukin-17 (IL-17) is associated with myocardial fibrosis and cardiac dysfunction in HF. IL-17D, a subtype of IL-17 originates from particular tissues such as the heart. However, there is very limited data on the IL-17 cytokine family in patients with HF. Therefore, we investigated the association between circulating IL-17D levels, clinical characteristics and outcome in a large cohort of patients with heart failure.

Methods and results: Plasma IL-17D was measured in 2032 patients with HF from 11 European countries using a proximity extension assay. The primary outcome was a composite of HF hospitalization or all-cause mortality. Patients with higher plasma IL-17D concentrations were more likely to have atrial fibrillation (AF), renal dysfunction and heart failure with preserved ejection fraction (HFpEF) and had higher plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations (all $p < 0.001$). IL-17D was not associated with interleukin-6 (IL-6) or C-reactive protein (CRP) concentrations. After adjustment for confounders in a multivariable Cox regression analysis, patients in the highest quartile of plasma IL-17D had a significantly increased risk of the composite outcome of HF hospitalization or all-cause mortality compared to patients in the lowest quartile [Hazard ratio (HR) 1.28, 95% confidence interval (CI) 1.05–1.57].

Conclusion: In patients with HF, elevated plasma IL-17D concentrations are associated with higher plasma NT-proBNP concentrations and a higher prevalence of AF and renal dysfunction. High IL-17D concentrations are independently associated with worse outcome.

1. Introduction

Heart failure (HF) is associated with cytokine activation and inflammation. Previous studies have mainly focused on the role of inflammatory cytokines, such as interleukin-1 (IL-1) and -6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [1]. Although randomized clinical trials in patients with heart failure and reduced ejection fraction (HFrEF) did not show beneficial effects of inhibition of TNF-α, a recent trial of infliximab, an antibody blocking interleukin-1β (IL-1β) activity reduced HF hospitalizations in patients with prior myocardial infarction and elevated C-reactive protein (CRP) [2,3]. A better understanding of the role of inflammation in heart failure could lead to the identification of novel treatment targets for heart failure.

Interleukin-17 (IL-17) is a pro-inflammatory cytokine mainly

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Table 1
Baseline characteristics. Data are mean (SD), n (%), or median (IQR). BMI, body-mass index; NYHA,New York Heart Association.; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease.

	IL-17D 1st Quartile *N* = 508	IL-17D 2nd Quartile N = 508	IL-17D 3rd Quartile N = 508	IL-17D 4th Quartile N = 508	*p*-value
Female sex, n (%)	117 (23.0%)	135 (26.6%)	127 (25.0%)	159 (31.3%)	**0.021**
Age (years), mean (SD)	62.8 (12.3)	67.3 (11.8)	70.8 (10.3)	74.4 (10.4)	**<0.001**
BMI (kg/m^2), mean (SD)	28.2 (5.7)	28.1 (5.5)	27.8 (5.6)	27.2 (5.1)	**0.012**
NYHA class					0.062
I	15 (3.1%)	6 (1.2%)	11 (2.2%)	10 (2.0%)	
II	197 (40.4%)	185 (37.2%)	183 (37.2%)	159 (32.2%)	
III	212 (43.4%)	253 (50.9%)	233 (47.4%)	265 (53.6%)	
IV	64 (13.1%)	53 (10.7%)	65 (13.2%)	60 (12.1%)	
LVEF (%), mean (SD)	29.6 (9.7)	30.8 (10.0)	31.2 (10.9)	33.0 (11.9)	**<0.001**
Type of Heart Failure, n (%)					**<0.001**
HFrEF	423 (93.0%)	404 (90.8%)	404 (88.6%)	380 (83.0%)	
HFmrEF	14 (3.1%)	17 (3.8%)	22 (4.8%)	29 (6.3%)	
HFpEF	18 (4.0%)	24 (5.4%)	30 (6.6%)	49 (10.7%)	
Systolic blood pressure (mmHg), mean (SD)	124 (24)	125 (22)	125 (21)	126 (23)	0.53
Heart rate (bpm), mean (SD)	82 (21)	80 (20)	80 (20)	79 (19)	0.14
Pulm. cong./ oedema with rales/crackles, n (%)					
No	234 (47.9%)	237 (48.2%)	218 (43.9%)	232 (46.7%)	0.65
Single base	56 (11.5%)	57 (11.6%)	63 (12.7%)	70 (14.1%)	
Bi-basilar	199 (40.7%)	198 (40.2%)	216 (43.5%)	195 (39.2%)	
Extent of peripheral oedema, n (%)					
Not Present	185 (45.0%)	184 (43.0%)	164 (38.3%)	166 (39.8%)	
Ankle	123 (29.9%)	129 (30.1%)	121 (28.3%)	114 (27.3%)	0.22
Below Knee	81 (19.7%)	84 (19.6%)	107 (25.0%)	102 (24.5%)	
Above Knee	22 (5.4%)	31 (7.2%)	36 (8.4%)	35 (8.4%)	
Orthopnoea present, n (%)	170 (33.5%)	175 (34.6%)	179 (35.2%)	172 (33.9%)	0.94
Previous HF hosp. in last year, n (%)	135 (26.6%)	161 (31.7%)	165 (32.5%)	164 (32.3%)	0.13
Hypertension, n (%)	286 (56.3%)	312 (61.4%)	318 (62.6%)	338 (66.5%)	**0.009**
Atrial fibrillation, n (%)	178 (35.0%)	205 (40.4%)	251 (49.4%)	291 (57.3%)	**<0.001**
Myocardial Infarction, n (%)	192 (37.8%)	185 (36.4%)	185 (36.4%)	194 (38.2%)	0.91
Diabetes, n (%)	143 (28.1%)	169 (33.3%)	169 (33.3%)	164 (32.3%)	0.24
COPD, n (%)	94 (18.5%)	88 (17.3%)	89 (17.5%)	76 (15.0%)	0.49
Peripheral arterial disease, n (%)	52 (10.2%)	58 (11.4%)	55 (10.8%)	59 (11.6%)	0.90
Stroke, n (%)	37 (7.3%)	48 (9.4%)	52 (10.2%)	56 (11.0%)	0.20
Renal disease, n (%)	99 (19.5%)	135 (26.6%)	151 (29.7%)	190 (37.4%)	**<0.001**
Smoking					
None	142 (28.0%)	178 (35.1%)	203 (40.0%)	217 (42.8%)	
Past	260 (51.2%)	255 (50.3%)	231 (45.6%)	246 (48.5%)	**<0.001**
Current	106 (20.9%)	74 (14.6%)	73 (14.4%)	44 (8.7%)	
Hemoglobin (g/dL), mean (SD)	13.3 (1.9)	13.2 (1.9)	13.3 (1.8)	12.9 (2.0)	**0.002**
Serum Creatinine (μmol/L), median (IQR)	93 (79, 115)	100 (83, 124)	103 (85, 133)	113 (92, 148)	**<0.001**
eGFR (CKD-EPI) (mL/min/1.73 m2), mean (SD)	70 (22)	63 (22)	60 (22)	52 (21)	**<0.001**
Sodium (mmol/L), median (IQR)	139 (137, 141)	139 (137, 141)	140 (137, 142)	140 (137, 142)	**0.013**
Potassium (mmol/L), median (IQR)	4.2 (3.9, 4.5)	4.3 (3.9, 4.6)	4.2 (3.9, 4.6)	4.2 (3.9, 4.6)	0.23
NT-proBNP (pg/mL), median (IQR)	2080 (943, 4397)	2478 (1006, 5010)	2874 (1362, 6230)	3515 (1710, 7751)	**<0.001**
CRP (mg/L), median (IQR)	14.5 (6.3, 27.6)	13.6 (6.1, 27.1)	13.3 (5.8, 25.7)	11.9 (5.8, 27.9)	0.80
IL-6 (pg/mL), median (IQR)	4.9 (2.5, 9.6)	5.1 (2.7, 10.2)	5.4 (3.0, 10.1)	5.3 (3.2, 10.1)	0.12

produced by T lymphocytes and induces the production of inflammatory cytokines like IL-1β, IL-6 and TNF-α [4–6]. The IL-17 family includes six members (IL-17 A-F) that all participate in both acute and chronic inflammatory processes [7]. In animal HF models, IL-17 was upregulated and influenced myocardial remodelling [8,9]. Interleukin-17D (IL-17D) as one of the subtypes of the IL-17 family is preferentially expressed in the heart [5]. However, there is a paucity of data on the IL-17 cytokine family in patients with HF.

We therefore investigated the clinical characteristics and outcome associated with increased plasma concentrations of IL-17D in a large cohort of patients with heart failure.

2. Methods

IL-17D concentrations were measured in plasma of 2032 patients with HF enrolled in the BIOSTAT-CHF registry which has been described presviously [10]. In short, BIOSTAT-CHF is a multinational, prospective, observational cohort study that included patients with worsening heart failure from 11 European countries. Inclusion criteria were age>18, symptoms of new-onset or worsening HF and either left ventricular ejection fraction (LVEF) of ≤40% or elevated levels of B-type natriuretic peptide (BNP) and/or N-terminal pro-B-type natriuretic peptide (NT-proBNP). Moreover, all participants had to be treated with either oral or intravenous furosemide ≥40 mg/day or equivalent at the time of inclusion. Furthermore, the patients were required to be sub-optimally treated with guideline recommended therapy with the prospect of initiation of uptitration of guideline-recommended therapy.

Plasma IL-17D was measured using the Olink® Target 96 Cardiovascular II kit. This method uses a proximity extension assay (PEA) technology providing normalized protein expression data wherein a high protein value corresponds to a high protein concentration, but not an absolute quantification.

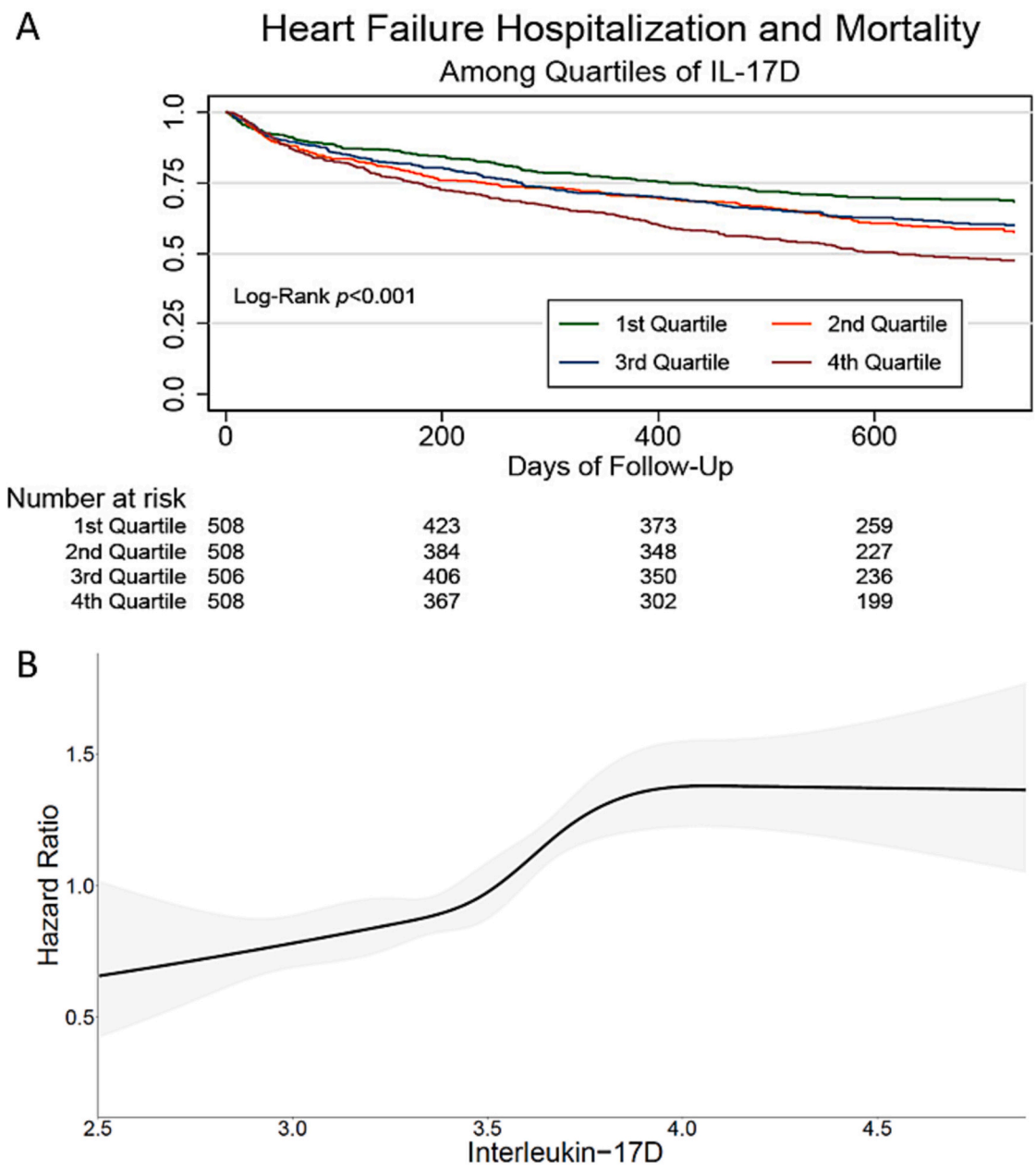

Fig. 1. Kaplan-Meier estimates according to IL-17D quartile level (A) and restricted cubic spline model with five knots for the combined endpoint of heart failure hospitalizations and mortality according to continuous levels of IL-17D (B).

IL-17D levels were divided into quartiles. Clinical characteristics were compared using one-way analysis of variance (ANOVA), the Kruskal–Wallis test and the Chi-square test, where appropriate. The primary outcome was the composite outcome of hospitalization for HF or all-cause mortality. Kaplan-Meier curves and the Log-rank test were used to test and display differences in outcome between IL-17D quartiles. Furthermore, we implemented restricted cubic splines modelling to visualize the association between continuous IL-17D levels and outcome. Cox proportional hazard regression analysis was used to investigate multivariable associations of plasma IL-17D quartiles with the primary outcome because of a non-linear association of IL-17D levels with outcome. We corrected for clinical confounders such as age, sex and the BIOSTAT-CHF risk model for predicting HF hospitalization or mortality which includes age, NT-proBNP, hemoglobin, the use of a beta-blocker at time of inclusion, a HF hospitalization in the year before inclusion, peripheral oedema, systolic blood pressure, high-density lipoprotein and sodium and has been published previously [11]. Furthermore, we also corrected for plasma IL-6 to investigate its additional influence on the outcome.

3. Results

Baseline characteristics of the 2032 patients with HF are displayed in Table 1 according to quartiles of IL-17D. Patients with high IL-17D levels were older, more often women and had higher left ventricular ejection fraction (LVEF). They were more likely to have hypertension, atrial fibrillation (AF) and renal dysfunction. Furthermore those patients had higher plasma NT-proBNP concentrations and more often heart failure with preserved ejection fraction (HFpEF) (Table 1). However, IL-17D was not associated with IL-6 or CRP concentrations.

In Kaplan-Meier analysis (Fig. 1A) as well as in restricted cubic splines modelling (Fig. 1B), a higher risk for the primary outcome of HF hospitalization or death was observed with higher levels of IL-17D. Spline analysis showed a non-linear relationship between IL-17D and

Table 2
Cox regression combined endpoint of heart failure hospitalizations and mortality.

Subgroup	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
1st Quartile	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
2nd Quartile	1.39 (1.13–1.72)*	1.25 (1.01–1.55) *	1.22 (0.99–1.51)	1.22 (0.98–1.51)
3rd Quartile	1.32 (1.06–1.63)*	1.08 (0.87–1.35)	1.03 (0.83–1.27)	1.01 (0.82–1.26)
4th Quartile	1.86 (1.52–2.28)*	1.42 (1.15–1.76)*	1.28 (1.05–1.57)*	1.24 (1.01–1.53)*

Model 1: Unadjusted.
Model 2: Adjusted for Age and Sex.
Model 3: Adjusted for BIOSTAT-CHF risk model (age, NT-proBNP, hemoglobin, the use of a beta-blocker at time of inclusion, HF hospitalization in the year before inclusion, peripheral oedema, systolic blood pressure, high-density lipoprotein and sodium).
Model 4: Adjusted for BIOSTAT-CHF risk model and IL-6 (log).
* $p < 0.05$.

the primary outcome (Fig. 1B). In Cox proportional hazard regression analysis, compared to patients in the lowest quartile of IL-17D levels, patients in the highest quartile had an increased risk of the primary combined outcome of HF hospitalization or death [HR (95% CI): 1.86 (1.52-2.28); Table 2]. After adjustment for potential confounders from the BIOSTAT-CHF risk prediction model those patients still had a significantly higher risk of the primary combined outcome [HR (95% CI): 1.28 (1.05–1.57); Table 2]. Also after additional adjustment for IL-6 levels this association remained significant [HR (95% CI): 1.24 (1.01–1.53); Table 2].

4. Discussion

In a large patient cohort with HF, elevated plasma IL-17D concentrations were associated with older age, elevated plasma NT-proBNP concentrations and a higher prevalence of AF, hypertension, renal dysfunction and HFpEF. Furthermore, high plasma IL-17D concentrations were independently associated with a greater risk of heart failure hospitalization or death.

Smaller studies have shown that patients with HF had higher plasma IL-17 concentrations than controls without heart failure [12,13]. This is the first study that investigates clinical characteristics and prognosis of patients with heart failure according to plasma concentrations of IL-17D.

We showed that patients with higher IL-7D concentrations had a higher left ventricular ejection fraction and more often had heart failure with preserved ejection fraction. These data confirm previous studies demonstrating that inflammation is more pronounced in patients with HFpEF than in those with HFrEF [14–16]. These inflammatory processes are likely driven by certain comorbidities [17]. Interestingly, we found that patients with higher plasma IL-17D concentrations had a higher prevalence of these comorbidities, such as renal dysfunction, AF and hypertension.

IL-17 is produced by T lymphocytes and induces inflammatory cytokines, such as IL-1β, IL-6 and TNF-α [6,18]. However, in contrast to our expectation, we did not find differences in CRP and IL-6 levels between quartiles of IL-17D, possibly because IL-17D exerts its effects locally in specific tissues such as the heart [5]. If true, IL-17D might play an essential role in cardiac-specific inflammation and be a cardiac-specific inflammatory biomarker. In animal HF models, knock-out of IL-17 attenuated cardiac fibrosis and improved cardiac function [8,19]. Although causality cannot be ascribed in an observational study, our findings in combination with pre-clinical studies might provide a rationale for developing anti-IL17 therapies for HF. Further research is needed to investigate the role of the IL-17 cytokine family in HF pathophysiology and its potential as a therapeutic target in patients with HF.

Declaration of Competing Interest

A.A.V. has received research support or consultancy fees from Amgen, AstraZeneca, Bayer AG, Boehringer Ingelheim, Cytokinetics, Merck, Myokardia, Novo Nordisk, Novartis and Roche Diagnostics. M.M. has received personal fees from Vifor Pharma, Amgen, AstraZeneca, Abbott Vascular, Bayer, Servier, Edwards Therapeutics, Actelion, LivaNova, and Windtree Thera-peutics. J.T. is supported by the National University of Singapore Start-up grant, the tier 1 grant from the ministry of education and the CS-IRG New Investigator Grant from the National Medical Research Council; has received consulting or speaker fees from Daiichi-Sankyo, Boehringer Ingelheim, Roche diagnostics and Us2.ai, owns patent US-10702247-B2 unrelated to the present work. P.v.d.M. is supported by a grant from the European Research Council (ERC CoG 101,045,236, DISSECT-HF) The UMCG, who employs PvdM received consultancy fees and/or grants from Novartis, Pharmacosmos, Vifor Pharma, Astra Zeneca, Pfizer, Pharma Nord, BridgeBio, Novo Nordisk and Ionis. J.C. reports grants from British Heart Foundation; personal fees from Abbott, personal fees from Amgen, grants and personal fees from Bayer, grants and personal fees from Bristol Myers Squibb, personal fees from Novartis, personal fees from Medtronic, personal fees from Idorsia, grants and personal fees from Pharmacosmos. grants and personal fees from Vifor, personal fees from Servier, personal fees and non-financial support from Boehringer-Ingelheim, personal fees from Astra-Zeneca, personal fees from Biopeutics, personal fees from Moderna, grants and personal fees from Viscardia, personal fees and non-financial support from NI Medical, grants from Pharma Nord. C.C.L. has received educational grants and/or consulting fees from Applied Threapeutics, Astra Zeneca, Boehringher Ingelheim. Lexison, MSD. Menarini, Moderna, Novartis, Novo Nordisk and Vifor.

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