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Syndecan-1 as an independent risk factor for the incidence of adverse cardiovascular events in patients having stage C and D heart failure with non-ischemic dilated cardiomyopathy

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ABSTRACT

Background: Patients with heart failure (HF) having non-ischemic dilated cardiomyopathy (DCM) have high mortality rates. Syndecan-1 is reportedly associated with cardiac fibrosis and inflammation. This study explored the role of syndecan-1 in patients with non-ischemic DCM.

Methods: Patients with HF were prospectively enrolled. Comprehensive clinical and biochemical analysis were performed. All patients were followed up for composite of major adverse cardiac events of cardiovascular death and cardiac transplantation.

Results: We measured syndecan-1 levels in 96 patients with HF and non-ischemic DCM. The primary outcome was the 3-year major adverse cardiac events. Approximately, 71% of patients were men with mean age and LVEF of 51.08 ± 13.28 years and 31.90 ± 8.85%, respectively. Median syndecan-1 levels were 456.57 pg/ml (interquartile range, 244.93–1181.26 pg/ml). Multivariate Cox regression analysis for Model I (adjusted for age, sex) and II (adjusted for traditional confounding factors) revealed that baseline syndecan-1 remained an independent predictor of composite endpoint events (Model I HR, 1.10/100 pg/ml increase in syndecan-1 level, 95% CI, 1.04–1.16, $P = 0.0006$; Model II HR, 1.10/100 pg/ml increase in syndecan-1 level, 95% CI, 1.03–1.18, $P = 0.0029$). Kaplan Meier analysis based on syndecan-1 tertiles revealed that the top tertile was associated with reduced survival compare to that in middle and bottom tertiles ($P < 0.0001$). Multivariate logistic regression analyses showed a positive correlation between syndecan-1 level and fibrosis and inflammatory markers.

Conclusion: In patients with HF and non-ischemic DCM, the syndecan-1 level is important in the assessment of risk of adverse clinical outcome, and syndecan-1 level is correlated with fibrosis and inflammatory biomarkers.

1. Introduction

The prognosis in heart failure patients with non-ischemic dilated cardiomyopathy (DCM) remains poor despite advances in medical therapy and the introduction of cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillators (ICDs) [1,2]. Recently, results from the DANISH Study (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality) [3] have failed to show that patients with DCM may benefit from an ICD. This may indicate that low left ventricular ejection fraction (LVEF), a key criterion for selecting patients with ischemic heart disease (IHD) for an ICD [4] is not suitable for risk stratification in DCM. However, accurate identification of patients with poor prognosis is required to ensure improvement in outcomes and wise use of resources in DCM with non-ischemic systolic heart failure.

Myocardial fibrosis is a substrate for ventricular arrhythmia and is associated with cardiac remodeling and adverse cardiac events [5]. However, precise and reliable techniques to define the type and amount of fibrosis associated with outcomes are lacking. Although studies and meta-analyses reported that late gadolinium enhancement (LGE) detected by cardiovascular magnetic resonance (CMR) may be a useful marker for predicting major adverse cardiovascular events in patients

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with cardiomyopathy [6–8], assessment of cardiac fibrosis with CMR is currently not part of the routine clinical work-up of patients with non-ischemic cardiomyopathy. Blood biomarkers could be useful for the estimation of cardiac fibrosis in well-defined patient groups.

Syndecan-1 is also a promising prognostic biomarker in heart failure. Syndecan-1 belongs to the family of transmembrane proteoglycans and is believed to regulate cardiac fibrosis [9]. Animal studies have suggested that syndecan-1 expression is induced by tissue injury and regulates inflammatory and reparative responses [10]. Human studies have shown that patients with higher circulating syndecan-1 levels had poor renal function [11]. Circulating syndecan-1 levels are also correlated with markers of fibrosis and remodeling [11]. Doubling of the syndecan-1 levels was associated with an increased risk of all-cause mortality and re-hospitalization in patients with heart failure and preserved ejection fraction (HFpEF) [12]. However, the prognostic value of syndecan-1 in patients with heart failure and reduced ejection fraction (HFrEF) remains debatable [11,12], and its value in patients having non-ischemic systolic heart failure with DCM is untested.

2. Methods

2.1. Patient population and study design

Between January 1 and August 31, 2015, consecutive patients with stage C or D HFrEF were prospectively identified and enrolled into the observational cohort study in the Department of Heart Failure Program at Anzhen Hospital (Capital Medical University of Beijing, China). The study enrolled 146 patients having HFrEF [4] with DCM as defined by the World Health Organization/International Society and the Federation of Cardiology criteria [13]. Inclusion criteria of the study included patients with stage C or D heart failure [14,15], LVEF < 40%, and left ventricular end-diastolic diameter (LVEDD) > 60 mm on echocardiography. Exclusion criteria included patients with congenital heart disease, infiltrative cardiomyopathy (i.e., sarcoidosis and amyloidosis), valvular heart disease, acute myocardial infarction (AMI) within 1 month, or a history of CRT and ICD implantation. All enrolled patients underwent a comprehensive clinical evaluation, coronary angiography. Forty-six patients with ischemic heart disease (IHD) who showed > 50% narrowing of the coronary artery lumen on coronary angiography (CA) or with a history of MI, and four patients without blood samples were further excluded. DCM may have been idiopathic, familial/genetic, viral, and/or immune, or alcoholic/toxic [13]. The final analysis included 96 patients with stage C or D non-ischemic systolic heart failure (Fig. 1). This study protocol was approved by the Human Subjects Review Committee at Anzhen Hospital. All the experiments were performed in accordance with relevant guidelines and regulations.

2.2. End-points

The primary outcome of the present study was the composite of major adverse cardiac events (MACE), including cardiovascular death and cardiac transplantation based on information obtained from medical records and telephone calls. A telephone interviewer inquired about the patient status of each patient (or representative) every 6–9 months. Two physicians reviewed all medical records for outcome diagnosis and assignments of event dates. The patients were followed up until April 2018.

2.2.1. Biochemical analysis

EDTA tubes were used to collect blood that was centrifuged at 3000 rpm for 10 min at room temperature. The plasma thus obtained was used directly or stored at −80 °C for later measurement. N-terminal pronatriuretic peptide (NT-proBNP), syndecan-1, Gal-3. and ST-2 levels were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA) based on the manufacturer's instructions.

Human syndecan-1 DuoSet ELISA (R&D Systems) was used to measure syndecan-1 levels, and the lower detection limit for syndecan-1 was 125.0 pg/ml with an upper detection limit was 8000 pg/ml. Syndecan-1 was measured in stored plasma samples from all study participants. The 96-well microplates were coated with 100 µl per well of the diluted Capture Antibody (R&D Systems), and incubated with 100-µl samples or standards (serial dilutions of recombinant syndecan-1, R&D Systems), followed by incubation with diluted streptavidin-HRP (Horseradish Peroxidase) (R&D Systems). The bound antibodies were detected with streptavidin-HRP, and the reaction was stopped with H_2SO_4; then, optical density was determined. If wavelength correction was available, wavelength was set to 540 or 570 nm. If wavelength correction was not available, readings at 540 or 570 nm were subtracted from the readings at 450 nm.

2.2.2. Statistical analysis

We first compared data distribution of each covariate among syndecan-1 tertiles, using analysis of variance (normal distribution) or Kruskal–Wallis rank sum test (non-normal distribution) for continuous variables, and χ^2 test was used for categorical data (Table 1). Subsequently, univariate and multivariate Cox regression models (Tables 2 and 3) were used to examine whether syndecan-1 and other covariates had an independent effect on MACE during the 3-year follow-up, separately. Univariate Cox regression analyses were used to examine all significant variables. We also adjusted for variables that, when added to this model changed the matched hazard ratio by at least 10%. Trend tests were computed by modeling the syndecan-1 tertiles as continuous variables. Subsequently, survival estimates and cumulative event rates were compared using the Kaplan–Meier method by using the time-to-first event for each endpoint. The log-rank test was used to compare the Kaplan–Meier hazard ratios (HR) for adverse events, and their corresponding 95% confidence intervals (CIs) (Fig. 2). Finally, logistic regression models were constructed to establish clinical determinants of syndecan-1 levels and its relationship to other markers of inflammation and fibrosis (Supplementary Table S1–S2). Meanwhile, we adjusted for variables that changed the matched hazard ratio by at least 10% when added to the model. All data were double entered and exported to tab-delimited text files. All analyses were performed using Empower (R) (http://www.empowerstats. com, X&Y solutions, Inc) and R (http://www.R- project.org).

3. Results

3.1. Patients characteristics

The final analysis included 96 patients with non-ischemic DCM with stage C or D heart failure (Fig. 1). The patients were divided based on the tertiles of baseline syndecan-1 concentrations. The baseline demographic and admission biochemical characteristics are presented by syndecan-1 tertiles in Table 1. The mean age of the 96 patients with non-ischemic DCM with stage C or D heart failure was 51 y (51.08 ± 13.28 y) at admission, and 71 of the these patients (73.96%) were men. The mean LVEF on echocardiography was 31.90% ± 8.85%, and all patients had either stage C or D heart failure at presentation. Moreover, 46 (47.92%) patients had previous hypertension, 20 (20.83%) had previous diabetes mellitus, and 9 (9.38%) had chronic kidney dysfunction. On electrocardiogram, atrial fibrillation was observed in 22.11% of patients with heart failure. The mean calculated NT-proBNP was 84.35 ± 12.22 ng/ml. No difference was found in patients' age, sex, body mass index (BMI), and LVEF between the higher and lower syndecan-1 level groups. In addition, baseline syndecan-1 concentrations were directly associated with blood urea nitrogen (BUN), levels of fibrosis and inflammatory markers, and history of diabetes mellitus. Interestingly, no increase levels of NT-proBNP were observed in patients with higher syndecan-1 levels. Among the

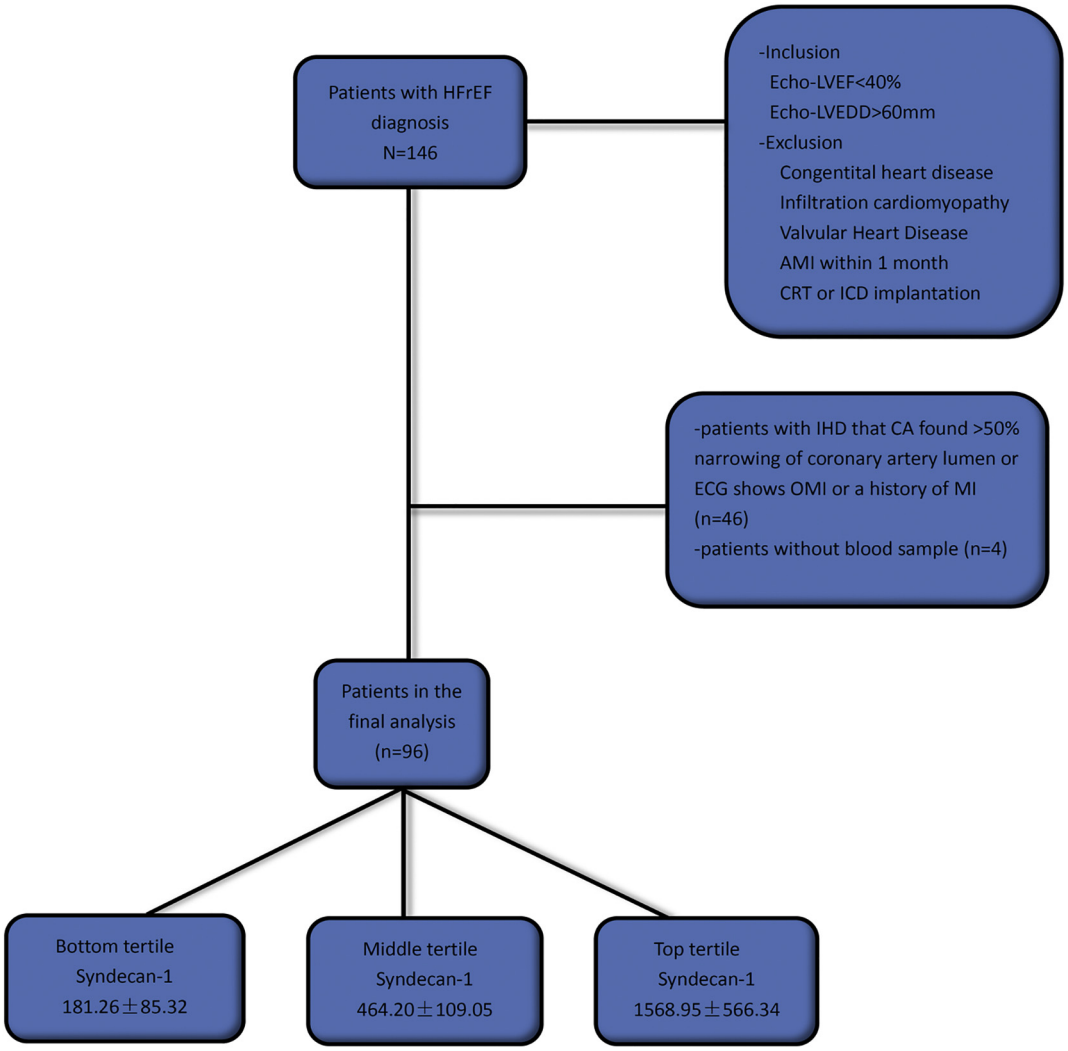

Fig. 1. Flow chart of patients with non-ischemic heart failure with stage C or D HFrEF.

entire cohort, 94.79% of patients were prescribed either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker, 95.0% were prescribed a beta-blocker, 91.67% were prescribed an aldosterone antagonist, 94.79% were prescribed loop diuretics, and 8.33% were prescribed digoxin.

3.2. Syndecan-1 and clinical outcome in patients with non-ischemic DCM with stage C or D heart failure

During the mean 937-day follow-up period (937 ± 278 days), 17 (17.71%) patients developed major adverse cardiac events: 15 patients died and 2 patients underwent cardiac transplantation. The results of the univariate analyses of major adverse events during the follow-up period are summarized in Table 2. Univariate analyses showed that renal function, syndecan-1, and sodium and galectin-3 in blood at admission were associated with significant increase in the incidence of adverse cardiovascular events. We performed a multivariate Cox regression analysis to further explore syndecan-1 level as a long-term prognostic marker. In the multivariable analysis shown in Table 3, syndecan-1 concentration was the independent risk factor for major adverse cardiac events in Model I (HRadj 1.10/100 pg/ml increase, 95% CI, 1.04–1.16, $P = 0.0006$) after adjusting for patients' age and sex, and in Model II (HRadj 1.10/100 pg/ml increase, 95% CI 1.04–1.17, $P = 0.0016$) after adjusting for patients' age, sex, BUN, sodium, galectin-3 and ST2. Kaplan–Meier survival analysis (Fig. 2) showed a significant difference among patients stratified by syndecan-1 tertile that syndecan-1 in top tertile was associated with reduced survival than in middle and bottom tertile (log-rank, $P < 0.0001$).

3.3. Predictors of syndecan-1 levels in patients with stage C or D heart failure

Supplementary Tables S1–S2 shows the logistic regression analysis to assess whether syndecan-1 (based on syndecan-1 levels, top tertile vs middle and bottom tertile) was associated with fibrosis or inflammation. Univariate logistic regression analyses showed that BUN, high-sensitive C-reactive protein (hsCRP), Gal-3, ST2 in blood, and history of diabetes mellitus were significantly associated with higher syndecan-1 levels in patients with no-ischemic DCM with stage C or D heart failure (Supplementary Tables S1). No correlation could be observed between syndecan-1 and NT-proBNP. We also performed a multivariate logistic regression analysis to further explore predictors of syndecan-1 levels in patients with no-ischemic DCM with stage C or D heart failure. In the multivariable analysis shown in Supplementary Tables S2, the higher syndecan-1 levels in patients with no-ischemic DCM with stage C or D heart failure were related to fibrosis markers of Gal-3 and ST-2 and inflammatory markers, such as hsCRP in Model I (RRadj, 1.29; 95% CI, 1.07–1.55, $P = 0.0066$; RRadj, 1.07; 95% CI, 1.02–1.12; $P = 0.0044$; RRadj, 1.07; 95% CI, 1.00–1.14; $P = 0.0427$; respectively.) after adjusting for patients' age and sex, and in Model II (RRadj, 1.28; 95% CI,

Table 1
Clinical and biochemical characteristics of the patients with stage C or D heart failure based on syndecan-1 concentration.

	All patients (n = 96)	Bottom tertile (n = 32)	Middle tertile 2 (n = 32)	Top tertile 3 (n = 32)	*P* value
Syndean-1 (pg/ml)	738.14 ± 687.87	181.26 ± 85.32	464.20 ± 109.05	1568.95 ± 566.34	< 0.001
Age, mean(SD) (y)	51.08 ± 13.28	51.97 ± 13.63	48.81 ± 12.51	52.47 ± 13.77	NS
Male (%)	71 (73.96%)	21 (65.62%)	24 (75.00%)	26 (81.25%)	NS
BMI, mean(SD) (kg/m^2)	26.39 ± 4.71	25.86 ± 4.32	26.83 ± 4.45	26.52 ± 5.41	NS
Diabetes mellitus (%)	20 (20.83%)	3 (9.38%)	6 (18.75%)	11 (34.38%)	0.05
Hypertension (%)	46 (47.92%)	11 (34.38%)	20 (62.50%)	15 (46.88%)	NS
CKD (%)	9 (9.38%)	3 (9.38%)	3 (9.38%)	3 (9.38%)	NS
Atrial fibrillation (%)	21 (22.11%)	6 (18.75%)	6 (19.35%)	9 (28.12%)	NS
QRS duration, mean(SD)(ms)	133.05 ± 33.15	135.22 ± 34.17	130.39 ± 31.65	133.47 ± 34.39	NS
Morphology of QRS, (%)					NS
Normal	49 (52.13%)	16(50.00%)	19(63.33%)	14(43.75%)	
No-LBBB	21 (22.34%)	7(21.88%)	4(13.33%)	10(31.25%)	
LBBB	24 (25.53%)	9(28.12%)	7(23.33%)	8(25.00%)	
Echo-LVEDD, mean(SD)(mm)	67.29 ± 8.07	66.97 ± 8.45	67.19 ± 8.18	67.71 ± 7.80	NS
Echo-LVEF, (%)	31.90 ± 8.85	34.69 ± 12.11	30.03 ± 5.11	30.97 ± 7.39	NS
Hemoglobin, g/dl	142.67 ± 26.64	147.71 ± 18.68	136.54 ± 38.35	143.20 ± 18.95	NS
BUN, mean(SD) (mmol/l)	7.45 ± 2.64	6.76 ± 2.04	7.15 ± 1.92	8.47 ± 3.45	0.03
CK-MB (ng/ml)	2.20 ± 1.98	2.14 ± 2.02	1.94 ± 1.74	2.52 ± 2.19	NS
Glucose (mmol/l)	5.77 ± 1.45	5.45 ± 1.02	5.85 ± 1.51	6.04 ± 1.72	NS
Triglyceride (mmol/l)	1.43 ± 0.78	1.72 ± 1.00	1.24 ± 0.60	1.31 ± 0.60	NS
Cholesterol (mmol/l)	4.05 ± 0.94	4.36 ± 0.85	3.93 ± 1.11	3.86 ± 0.78	NS
Sodium (mEq/l)	139.65 ± 3.15	139.73 ± 2.40	139.81 ± 3.72	139.42 ± 3.33	NS
hsCRP (mg/dl)	6.38 ± 7.96	2.94 ± 5.30	7.14 ± 8.73	9.22 ± 8.43	0.01
NT-proBNP (ng/ml)	84.35 ± 21.22	85.90 ± 16.12	82.31 ± 26.08	84.86 ± 20.81	NS
Galectin 3 (ng/ml)	10.46 ± 3.47	9.32 ± 2.27	9.88 ± 2.98	12.20 ± 4.24	0.001
ST2 (ng/ml)	27.74 ± 14.26	24.62 ± 12.24	24.09 ± 11.33	34.51 ± 16.55	0.004
Medication					
ACEI (%)	78(81.25%)	23(71.88%)	29(90.62%)	26(81.25%)	NS
ARB (%)	13 (13.54%)	7(21.88%)	2(6.25%)	4(12.50%)	NS
Beta-blocker (%)	91(94.79%)	31(96.88%)	30(93.75%)	30(93.75%)	NS
Spironolactone (%)	88 (91.67%)	28(87.50%)	30(93.75%)	30(93.75%)	NS
Diuretics (%)	91 (94.79%)	29(90.62%)	30(93.75%)	32(100.00%)	NS
Digoxin (%)	8 (8.33%)	3(9.38%)	2(6.25%)	3(9.38%)	NS
Glinides (%)	4 (4.17%)	2 (6.25%)	1 (3.12%)	1 (3.12%)	NS
Metformin (%)	2 (2.08%)	1 (3.12%)	0 (0.00%)	1 (3.12%)	NS
α-Glucosidase inhibitors (%)	10 (10.42%)	4 (12.50%)	1 (3.12%)	5 (15.62%)	NS
Sulfonylurea (%)	3 (3.12%)	1 (3.12%)	1 (3.12%)	1 (3.12%)	NS
Insulin (%)	7 (7.29%)	1 (3.12%)	1 (3.12%)	5 (15.62%)	NS

CKD, chronic kidney disease; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; BUN, blood urea nitrogen; NT-proBNP, N-terminal probrain-type natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

1.05–1.55; $P = 0.0125$; RRadj, 1.06; 95% CI, 1.01–1.11; $P = 0.0131$; RRadj, 1.08; 95% CI, 1.01–1.16; $P = 0.0262$, respectively.) after adjusting for patients' age, sex, BUN, sodium, and history of diabetes mellitus.

4. Discussion

The present study evaluated an endothelial glycocalyx damage biomarker (syndecan-1) for the first time in patients with stage C or D heart failure and non-ischemic DCM. The syndecan-1 level had good discriminatory capacity for predicting major adverse cardiac events during the mean 937-day follow-up period (937 ± 278 days). Moreover, the association of syndecan-1 with long-term prognosis in patients with heart failure and non-ischemic DCM remained after adjusting for other traditional confounding factors.

Syndecan-1 (synd1) is a transmembrane heparin sulfate proteoglycan that functions as a coreceptor for growth factors and modulates signal transduction [16]. Synd1 has been shown to be an essential mediator of angiotensin II (ANGII) -induced cardiac fibrosis [16]. Animal studies have shown that the pro-fibrotic effects of synd1 in the heart are likely mediated through the renin-angiotensin-aldosterone-system (RAAS)-transforming growth factor-β (TGFβ)-connective tissue growth factor (CTGF)-Smad axis, affecting collagen matrix quantity and quality. In the extracellular milieu, synd1 associates with proteases that cleave off the ectodomain in a process termed shedding. Synd1shedding has been shown to regulate pathophysiological processes [17]. Synd-1 ectodomain also increased fibroblast proliferation and the release of TGFβ1 [18]. Shed synd-1 fragments are not only found in the ECM of tissues, but also in wound fluids and blood. The detection of syn1 fragments in blood raises the question of whether synd-1 can serve as a biomarker.

Several clinical studies investigated the significance of synd-1 in patients with heart failure. However, the conclusion of the study was controversial. Tromp et al. [12] analyzed plasma syndecan-1 levels in 567 patients with chronic heart failure. After 18 months of follow-up, the study found that a synd-1 level twice the cut-off value was associated with an increased risk of all-cause mortality and re-hospitalization in patients with HFpEF, but not in patients with HFrEF. Neves et al. investigated 201 patients with acute decompensated heart failure [11]. The study showed that the level of synd-1 was associated with in-hospital mortality rates and also showed a significant separation of 6-month survival curves for patients with low and high levels. Compared with two previous studies, our current research showed that the etiology of systolic cardiac dysfunction in all patients was non-ischemic DCM, and patients with ischemic cardiomyopathy (ICM) were excluded to eliminate confusion (Fig. 1). All selected patients had acute decompensation with stage C or D and LVEF < 40% on the echocardiogram, while patients with HFpEF were excluded. After the mean 937-day follow-up period (937 ± 278 days), synd-1 was found to be an independent risk factor for adverse cardiovascular events in the nearly homogeneous cohort of patients with non-ischemic DCM. This association was independent of traditional risk factors (Table 3). Our results also indicated that synd-1 in the top tertile of patients with heart failure and non-ischemic cardiomyopathy was associated with poor outcomes

Table 2
Univariate analysis for major adverse events in patients with stage C or stage D heart failure during a 3-y follow-up.

Variable	No. of event/No. of participants (%)	HR	95% CI	*P*-value
Age, mean (SD) (y)	17/96(17.71%)	1.03	0.99–1.06	NS
Sex (%)				
Male	13/71(18.31%)	Ref	–	–
Female	4/25(16.0%)	0.83	0.27–2.54	NS
BMI, mean(SD) (kg/m2)	17/96(17.71%)	0.97	0.88–1.08	NS
Diabetes mellitus (%)	4/20(20.0%)	1.18	0.38–3.61	NS
Hypertension (%)	8/46(17.39%)	0.94	0.36–2.42	NS
CKD (%)	1/9(11.11%)	0.60	0.08–4.53	NS
Heart rhythm				
Sinus rhythm	12/74(16.22%)	Ref	–	–
Atrial fibrillation	4/21(22.22%)	1.22	0.39–3.79	NS
QRS duration, mean (SD)(ms)	17/96(17.71%)	1.01	0.99–1.02	NS
Morphology of QRS, (%)				
Normal	6/49(12.24%)	Ref	–	–
No-LBBB	6/21 (40.82%)	2.47	0.80–7.66	NS
LBBB	4/24(16.67%)	1.41	0.40–5.01	NS
Echo-LVEDD, mean (SD)(mm)	17/96(17.71%)	1.04	0.99–1.10	NS
Echo-LVEF, (%)	17/96(17.71%)	0.95	0.88–1.01	NS
SBP (mmHg)	17/96(17.71%)	0.98	0.95–1.01	NS
HR bpm	17/96(17.71%)	0.99	0.96–1.02	NS
WBC (G/L)	17/96(17.71%)			
hsCRP (mg/dl)	17/96(17.71%)	1.00	0.94–1.07	NS
Hemoglobin, g/dl	17/96(17.71%)	1.00	0.98–1.02	NS
BUN, mean(SD) (mmol/l)	17/96(17.71%)	1.15	1.00–1.32	0.05
Sodium (mEq/l)	17/96(17.71%)	0.84	0.74–0.96	0.01
NT-proBNP (ng/ml)	17/96(17.71%)	0.99	0.97–1.02	NS
Galectin 3(ng/ml)	17/96(17.71%)	1.14	1.00–1.30	NS
ST2 (ng /ml)	17/96(17.71%)	1.01	0.98–1.04	NS
Syndecan-1 (per 100 pg/ml)	17/96(17.71%)	1.00	1.00–1.00	< 0.001
Syndecan-1 tertile				
Bottom t	2/32 (6.25%)	Ref	–	–
Middle t	2/32 (6.25%)	1.00	0.14–7.12	0.99
Top t	13/32 (40.62%)	8.26	1.86–36.63	0.006
P-value for trend		0.001		

CKD, chronic kidney disease; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; HR, heart rate.

(Fig. 2). To the best of our knowledge, this is the first study to demonstrate the prognostic value of synd-1 in patients with non-ischemic cardiomyopathy and HFrEF.

Finding a prognostic factor is important in patients with non-ischemic DCM. Recently, results from the DANISH Study (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heat Failure on Mortality) [3] failed to show that patients with DCM

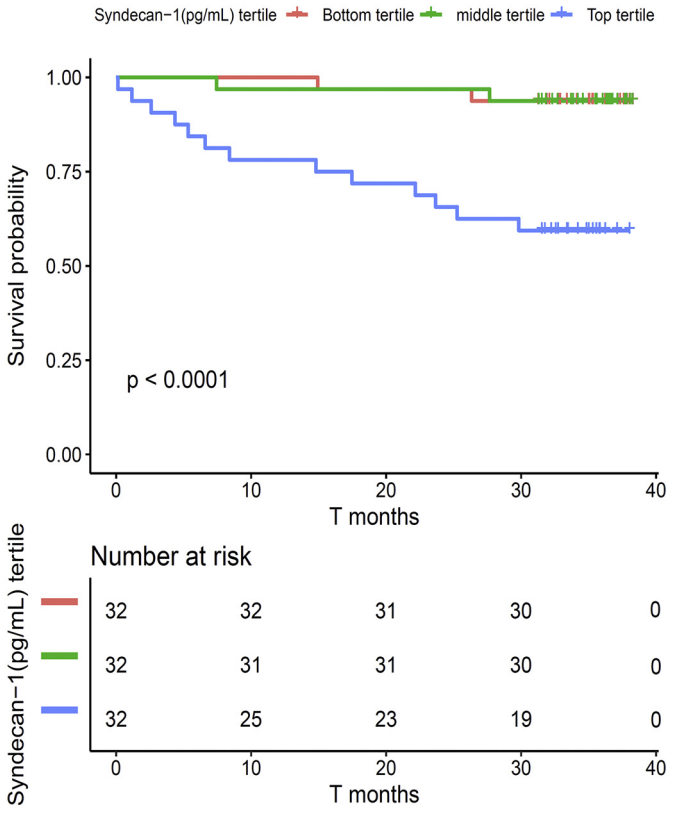

Fig. 2. Kaplan–Meier event-free survival curve. Kaplan–Meier analysis of freedom from major adverse cardiac events based on syndecan-1 tertile (log-rank, $P < 0.0001$).

may benefit from ICD. This may indicate that LVEF, a key criterion for selecting patients with ischemic heart disease for an ICD [4], is not suitable for risk stratification in non-ischemic DCM. Attention has recently focused on whether detection of myocardial fibrosis may assist with risk stratification in dilated cardiomyopathy [19]. Fibrosis is associated with contractile impairment, and provides a substrate for ventricular reentrant arrhythmia [7,8]. Tissue section histology has long been the gold standard for the analysis of fibrosis (i.e., collagen), offering distribution assessment (e.g., perivascular, interstitial, or focal accumulation), and quality assessment (e.g., collagen cross-linking). Since cardiac biopsies from patients are not readily available, histology has low clinical applicability with regards to the assessment of cardiac fibrosis. Although late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR) recently enables identification of myocardial fibrosis [20], assessment with CMR is currently not part of the routine clinical work-up of patients with non-ischemic cardiomyopathy.

Table 3
Multivariate Cox regression analysis with syndecan-1 concentration for major adverse cardiac events in patients with dilated cardiomyopathy with stage C or D heart failure during a 3-year follow-up.

	Univariate analysis	Model 1	Model 2
	HR 95% CI *P*-value	HR 95% CI *P*-value	HR 95% CI *P*-value
Syndecan-1 (per 100 pg/ml)	1.11 1.05–1.17 0.0001	1.10 1.04–1.16 0.0006	1.10 1.03–1.18 0.0029
Syndean-1(pg/mL) Tertile			
Bottom t	1.0	1.0	1.0
Middle t	1.00 0.14–7.12 0.9973	1.07 0.15–7.60 0.9486	1.00 0.14–7.33 0.9978
Top t	8.26 1.86–36.63 0.0055	7.82 1.76–34.80 0.0069	8.48 1.71–41.97 0.0088
Top t vs bottom t and middle t	8.24 2.68–25.32 0.0002	7.58 2.45–23.44 0.0004	8.49 2.34–30.79 0.0011
P-value for trend	0.0010	0.0017	0.0060

Model 1 adjust for: age, sex;
Model 2 adjust for: age, sex, BUN, sodium, Galectin 3, ST2.

Blood biomarkers could be useful for the estimation of cardiac fibrosis in well-defined patient groups. Our current research also demonstrated that synd-1 levels are correlated with fibrotic and remodeling markers, such as Gal-3, ST2, and inflammatory markers, such as hsCRP (Supplementary Table S2). This finding is consistent with that of previous studies [11,12]. However, we did not find a correlation between synd-1 and NT-proBNP.

5. Study limitations

Our present study has several limitations. First, it was performed in a single center and the study enrolled a relatively small number of patients. Second, there was no imaging analysis to correlate degree of fibrosis with biomarker levels because assessment of cardiac fibrosis with CMRI is currently not part of the routine clinical work-up of patients with heart failure. Furthermore, the specific cause of cardiovascular death was not discussed. However, because studies investigating the prognostic role of synd-1 in patients with heart failure are limited by conflicting results, our study is important to show that syndecan-1 can help guide therapy in patients with non-ischemic DCM.

6. Conclusions

In patients with non-ischemic dilated cardiomyopathy and HFrEF, synd-1 was an independent risk factor for the incidence of adverse cardiovascular events. Synd-1 levels strongly correlated with markers of fibrosis and inflammation. Further research is needed to address whether the intervention of the SDC-1 will affect the prognosis of patients with heart failure.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2018.12.022.

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