




# CILP1 as a biomarker for right ventricular dysfunction in patients with ischemic cardiomyopathy

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## Abstract

The aim of this study was to evaluate the cartilage intermediate layer protein 1 (CILP1) as a biomarker of right ventricular dysfunction in patients with ischemic cardiomyopathy (ICM). CILP1 plasma concentrations were measured in 98 patients with ICM and 30 controls without any cardiac abnormalities. All participants underwent cardiac magnetic resonance imaging. Median CILP1 concentrations were higher in ICM than in controls. In the tertile analysis, low right ventricular ejection fraction (RVEF) and high right ventricular end-systolic volume index and N-terminal pro-brain natriuretic peptide (NT-proBNP) were associated with higher CILP1 levels in ICM. However, there were no associations between CILP1 concentrations and left ventricular (LV) parameters in this group. In receiver-operating characteristic (ROC) analysis CILP1 was a good predictor of RVEF < 40% with an optimal cut-off value of 3545 pg/ml in ICM, whereas it was not predictive of LV ejection fraction (LVEF) < 40% (area under the curve [AUC] = 0.57). There was no significant difference between the ROC curves of CILP1 (AUC = 0.72) and NT-proBNP (AUC = 0.77) for RVEF < 40% ( $p = 0.42$ ). In multivariable regression analysis, RVEF was the only independent predictor of elevated CILP1. CILP1 and LVEF were the only independent predictors of RVEF < 40% in ICM. Our analysis demonstrates the potential role of CILP1 as a novel cardiac biomarker of prognostically relevant RV dysfunction in patients with ICM.

**Abbreviations:** CAD, coronary artery disease; CILP1, cartilage intermediate layer protein 1; CMR, cardiac magnetic resonance; DCM, dilated cardiac myopathy; ECM, extracellular matrix; ICM, ischemic cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; NT-proBNP, N-terminal pro-brain natriuretic peptide; PASP, systolic pulmonary artery pressure; PH, pulmonary hypertension; RV, right ventricular; RVEF, right ventricular ejection fraction; RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index; TAPSE, tricuspid annular plane systolic excursion; TGF- $\beta$ , transforming growth factor- $\beta$ .

Andreas Rolf and Till Keller contributed equally to this study.

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## KEYWORDS

fibrosis, MRI, myocardial remodeling, RVEF

## INTRODUCTION

A relevant number of patients with ischemic cardiomyopathy (ICM) have concomitant left ventricular (LV) and right ventricular (RV) dysfunction<sup>1</sup> and existing evidence shows that RV dysfunction is associated with adverse outcomes in these patients independently of LV function.<sup>2–5</sup>

Cardiac magnetic resonance (CMR) imaging is the established gold standard for the assessment of RV structure and function.<sup>6</sup> Ejection fraction of the RV (RVEF), a parameter reflecting systolic RV systolic (dys-)function, has been identified as an independent prognostic factor in ICM patients.<sup>2,4</sup> However, CMR is an expensive and time-consuming diagnostic modality that is also limited in its availability.<sup>7</sup>

Hence, biomarkers that can identify pathological RV remodeling and RV dysfunction in ICM could provide a simple and valuable diagnostic tool in the daily routine. Natriuretic peptides like N-terminal pro-B-type natriuretic peptide (NT-proBNP) are established prognostic biomarkers of LV and RV failure recommended by the current guidelines on acute and chronic heart failure<sup>8</sup> and pulmonary hypertension (PH).<sup>9</sup> However, natriuretic peptides are not RV specific and there are currently no established biomarkers with sufficient specificity for RV remodeling and function.

Cartilage intermediate layer protein 1 (CILP1) is an extracellular matrix (ECM) protein involved in pathological profibrotic signaling in the myocardium.<sup>10–12</sup> We recently demonstrated that CILP1 is associated with maladaptive RV remodeling in patients with PH. Furthermore, CILP1 concentrations were higher in PH patients with maladaptive RV remodeling as compared to cardiomyopathy patients and patients with LV hypertrophy without PH.<sup>13</sup>

The aim of this study was to analyze the association of plasma CILP1 concentrations with established prognostic CMR parameters of LV and RV structure and function in a cohort of ICM patients. It also aimed to evaluate the role of CILP1 as a biomarker of RV dysfunction in ICM in comparison to NT-proBNP.

## PATIENTS AND METHODS

## Study cohort

The present analysis uses patients enrolled in the ongoing cross-sectional study BioCVI that is part of the

Kerckhoff Biomarker Registry (BioReg) located in Bad Nauheim (Germany). The registry is approved by the local ethics committee, participation was voluntary, and all patients gave written informed consent. The BioCVI registry enrolls adult patients (>18 years old) with a clinical indication for CMR.<sup>14</sup>

For the present post hoc analysis, 98 patients with ICM and 30 controls enrolled in BioCVI between May 2016 and December 2020 were selected according to the following criteria:

ICM is defined as chronic coronary syndrome with prior myocardial infarction (MI), prior percutaneous coronary intervention (PCI) or prior coronary artery bypass surgery (CABG) and myocardial late gadolinium enhancement (LGE) in CMR.

This CMR-based ICM definition is based on previous evidence showing that LGE is an important prognosticator of significant coronary artery disease (CAD).<sup>15</sup>

However, the CMR-based ICM definition does not correspond to the established definitions of ICM, which also include LV systolic dysfunction.<sup>16–18</sup>

Hence, a subgroup analysis was additionally performed in 59 patients from the CMR-based ICM cohort with LV systolic dysfunction (left ventricular ejection fraction [LVEF]  $\leq 50\%$ ).

For the *control group*, patients without any right or left ventricular abnormalities according to the CMR were selected.

## Laboratory assessment

Venous blood samples were collected in all patients of the registry at enrollment in plain gel-filled tubes (Monovette; Sarstedt AG&Co.). Serum was processed immediately and frozen at  $-80^{\circ}\text{C}$  until assay.

CILP1 levels were determined using a high-sensitivity enzyme-linked immunosorbent assay (human CILP1 ELISA Kit; Cusabio Technology LLC) with a detection range of 93.75–6000 pg/ml, a minimum detectable concentration of 23.4 pg/ml, an intra-assay precision coefficient of variation  $<8\%$ , and an interassay precision coefficient of variation  $<10\%$ .

NT-proBNP levels were measured in serum with an electrochemiluminescence immunoassay using monoclonal antibodies (NT-proBNP assay; Roche Diagnostics). The intra-assay coefficients of variation are 1.5% and 1.3% at 124 and 14,142 ng/L, respectively, and the respective interassay coefficients of variation are 2.7%

and 1.7% at 125 and 32,930 ng/L, respectively, as shown by the package insert. The lower detection limit for the NT-proBNP assay is 5 ng/L.

## Cardiac imaging/MRI

Imaging was performed using a 3 Tesla scanner system (Magnetom Skyra; Siemens Healthcare) with a dedicated CMR protocol containing axial, coronal, and sagittal thoracic survey images, CINE sequences, steady-state-free precession sequences in two-, three-, and four-chamber views. The postprocessing was performed with syngo.via software package (Siemens Syngo; Siemens Healthcare).

All selected patients underwent transthoracic two-dimensional echocardiography as part of the clinical diagnostic work-up. Left and right ventricular assessment was performed as recommended by recent guidelines.

## Statistical analysis

Continuous variables are presented as mean  $\pm$  standard deviation (SD) or as median with 25th to 75th interquartile range, as appropriate. Categorical variables are expressed as numbers and percentages. Parametric distribution was assessed with the Shapiro–Wilk test. Normally distributed continuous variables were compared by the Welch two-sample *t* test and one-way analysis of variance with Bonferonni post hoc test. The Mann–Whitney *U* test and the Kruskal–Wallis test with Dunnet's post hoc test was used for non-normally distributed continuous variables. Receiver-operating characteristic (ROC) curve analysis was performed to assess the predictive value of CILP1, NT-proBNP for LVEF < 40%, and RVEF < 40%. The best CILP1 cut-off concentration for predicting RVEF < 40% was then selected based on the highest Youden index. Multi-variable logistic regression analyses were performed to identify independent predictors of RVEF < 40% and CILP1 concentrations greater than or equal to the estimated cut-off. A two-tailed *p* < 0.05 was considered to indicate statistical significance. Statistical analysis was performed using the R software package and SPSS Version 25.0.0 (SPSS Inc.).

## RESULTS

Clinical characteristics of the ICM patients (*n* = 98) compared to controls (*n* = 30) are presented in Table 1. All control patients had normal RV and LV dimensions

and function. ICM patients were more often male and older than controls.

Most patients in the ICM cohort had prior MI (86%) and 23% (*n* = 22) of these patients had an RVEF lower than 40%.

Patients with ICM showed a highly significant increase in median CILP1 (*p* < 0.001; Figure S1a) and NT-proBNP (*p* < 0.001; Figure S1b) concentration as compared to the controls.

Tertile analysis in the ICM cohort showed that patients with low RVEF (<45%) had higher CILP1 and NT-proBNP levels than those with high (>54%) or intermediate (45%–54%) RVEF, as well as controls (*p* < 0.05 for all comparisons; Figures 1a and S2a). Patients with high right ventricular end-systolic volume index (RVESVI) (>43 ml/m<sup>2</sup>) also showed higher CILP1 and NT-proBNP concentrations than patients in the low RVESVI tertile and controls (*p* < 0.05 for all comparisons; Figures 1b and S2b).

ICM patients without RV systolic dysfunction (RVEF > 50%, *n* = 51) had higher CILP1 and NT-proBNP levels than controls (*p* = 0.01 for CILP1 and *p* < 0.0001 for NT-proBNP). In this subgroup, NT-proBNP showed significant correlations with LVEF (*r* = 0.42, *p* = 0.003) and LVESVI (*r* = 0.32, *p* = 0.02), whereas there were no correlations between CILP1 and LV or RV parameters.

Interestingly, CILP1 and NT-proBNP also showed different associations with LV parameters in the entire cohort. CILP1 did not show any correlations to LV parameters. Furthermore, there were no significant differences in CILP1 concentrations between the low (<35%) and middle and high (>52%) LVEF tertiles (Figure 1c), as well as between the LVESVI tertiles (Figure 1d). Conversely, NT-proBNP concentrations in the low LVEF tertile were higher than in the other tertiles (*p* < 0.05 for middle vs. high and *p* < 0.001 for low vs. high; Figure S2c). ICM patients in the high LVESVI tertile also showed higher NT-proBNP concentrations than those in the low tertile (*p* < 0.01; Figure 2d).

CILP1 levels were higher in ICM patients in the high NT-proBNP tertile (>1800 pg/ml) than in the low tertile (<465 pg/ml, *p* < 0.001; Figure 2).

As expected, ROC curve analysis showed that NT-pro-BNP was a good predictor of a reduced LVEF (<40%) with an AUC of 0.80, whereas CILP1 yielded a low AUC of 0.57 (Figure 3a; *p* = 0.0004 for AUC<sub>CILP1</sub> vs. AUC<sub>NT-proBNP</sub>).

However, both CILP1 and NT-pro-BNP were good predictors of RVEF < 40% (Figure 3b). There were no significant differences between the two ROC curves (*p* = 0.42 for AUC<sub>CILP1</sub> vs. AUC<sub>NT-proBNP</sub> for RVEF < 40%).

**TABLE 1** Clinical characteristics

Variable	Controls (n = 30)	ICM (n = 98)	p Value
Age (year), median (IQR)	46 (29–53)	68 (60–76)	<0.001
Female sex, n (%)	17 (57)	23 (23)	0.001
BMI (kg/m <sup>2</sup> ), median (IQR)	25 (23–27)	27 (25–30)	0.001
BSA (m <sup>2</sup> ), median (IQR)	1.99 (1.73–2.08)	2.00 (1.88–2.16)	0.1
Cardiovascular risk factors			
Hypertension, n (%)	2 (7)	80 (82)	<0.001
Diabetes, n (%)	0 (0)	30 (31)	<0.001
Dyslipidemia, n (%)	2 (7)	70 (71)	<0.001
Smoking, n (%)	5 (19)	66 (68)	<0.001
Clinical history			
Chronic pulmonary disease, n (%)	3 (10)	15 (16)	0.44
CAD, n (%)	0 (0)	98 (100)	<0.001
Prior MI, n (%)	0 (0)	83 (86)	<0.001
Prior PCI, n (%)	0 (0)	73 (75)	<0.001
Prior CABG, n (%)	0 (0)	21 (22)	<0.001
Prior valvular surgery, n (%)	0 (0)	1 (1)	0.58
Atrial fibrillation, n (%)	1 (3)	30 (31)	0.001
Prior stroke TIA, n (%)	1 (3)	11 (11)	0.17
NYHA ≥ 3, n (%)	0 (0)	27 (35)	<0.001
Echocardiographic findings (only ICM)			
LVEF (%), median (IQR), n = 56	n.a.	40 (31–55)	
IVSd (mm), median (IQR), n = 49	n.a.	10 (44,451)	
LVPWd (mm), median (IQR), n = 47	n.a.	11 (44,451)	
RVEdD (mm), median (IQR), n = 47	n.a.	39 (30–44)	
TAPSE (mm), median (IQR), n = 54	n.a.	19 (16–22)	
PASP (mmHg), median (IQR), n = 43	n.a.	33 (31–36)	
MRI findings			
HF (1/min), median (IQR)	70 (61–84)	68 (60–75)	0.57
LVEF (%), median (IQR)	62 (60–67)	45 (31–57)	<0.001
LVEF < 40%, n (%)	0 (0)	41 (43%)	<0.001
LVESV (ml), median (IQR)	52 (42–73)	105 (69–164)	<0.001
LVESVI (ml/m <sup>2</sup> ), median (IQR)	30 (23–38)	51 (34–79)	<0.001
LVEDV (ml), median (IQR)	149 (128–181)	187 (150–246)	0.006
LVEDVI (ml/m <sup>2</sup> ), median (IQR)	81 (69–92)	91 (75–120)	<0.001
RVEF (%), median (IQR)	56 (52–60)	50 (41–58)	0.02
RVEF < 40%, n (%)	0 (0)	22 (23%)	<0.001
RVESV (ml), median (IQR)	62 (48–80)	77 (59–99)	0.008
RVESVI (ml/m <sup>2</sup> ), median (IQR)	33 (27–39)	38 (28–47)	0.03

TABLE 1 (Continued)

Variable	Controls (n = 30)	ICM (n = 98)	p Value
RVEDV (ml), median (IQR)	139 (115–169)	154 (123–177)	0.17
RVEDVI (ml/m <sup>2</sup> ), median (IQR)	76 (60–85)	76 (64–85)	0.81
Biomarker			
Creatinine (mmol/L), median (IQR)	0.72 (0.66–0.87)	0.91 (0.76–1.27)	<0.001
eGFR (ml/min/1.73 m <sup>2</sup> ), median (IQR)	99 (89–121)	86 (53–101)	0.001
NT-proBNP (pg/ml), median (IQR)	68 (32–100)	1000 (342–2463)	<0.001
CILP1 (pg/ml), median (IQR)	2919 (2436–3293)	4164 (2926–5429)	<0.001

Abbreviations: BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CILP1, cartilage intermediate layer protein 1; eGFR, estimated glomerular filtration rate; HF, heart frequency; ICM, ischemic cardiomyopathy; IQR, interquartile range; IVSd, diastolic interventricular septum thickness; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVPWd, diastolic left ventricular posterior wall thickness; MRI, magnetic resonance imaging; MI, myocardial infarction; n.a., not available; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide; PASP, pulmonary arterial systolic pressure; PCI, percutaneous coronary intervention; TAPSE, tricuspid annular plane systolic excursion; RVEF, right ventricular ejection fraction; RVEDd, right ventricular end-diastolic diameter; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume, RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index.

An optimal CILP1 cut-off value of 3545 pg/ml to identify RVEF < 40% was determined (90% sensitivity; 63% specificity). Characteristics according to this CILP1 threshold are given in Table 2. Patients with high CILP1 ( $\geq 3545$  pg/ml) had lower RVEF and higher RVESVI, NT-proBNP, and estimated glomerular filtration rate (eGFR) than those with low CILP1. There were no significant differences in terms of LV parameters.

In a binary logistic regression model adjusted for the parameters that showed the strongest association with high CILP1: NT-proBNP, RVEF, eGFR, and atrial fibrillation, only RVEF remained as an independent predictor of high CILP1 (Table 3a).

In a binary regression model adjusted for the parameters that showed the strongest association with RVEF < 40%: CILP1, NT-proBNP, and LVEF, the parameters CILP1 and LVEF were the only independent predictors of a reduced RVEF (Table 3b).

Subgroup analyses in ICM patients with LVEF  $\leq 50\%$  (based on the CMR data) also showed significant associations of higher CILP1 with low RVEF and high RVESVI ( $p < 0.05$  for all comparisons; Figure S4a,b), whereas there were no associations with low LVEF and high LVESVI in the tertile analysis ( $p < 0.05$  for all comparisons; Figure S4c,d). Higher NT-proBNP was associated with low RVEF (Figure S5a) and LVEF (Figure S5c), as well as with high RVESVI (Figure S5b) and LVESVI (Figure S5d). ROC analyses in this subgroup confirmed CILP1 (AUC = 0.74) and NT-proBNP (AUC = 0.73) as good predictors of RVEF < 40% (Figure S6b). CILP1 remained a poor predictor of LVEF < 40% (AUC = 0.63; Figure S6a).

## DISCUSSION

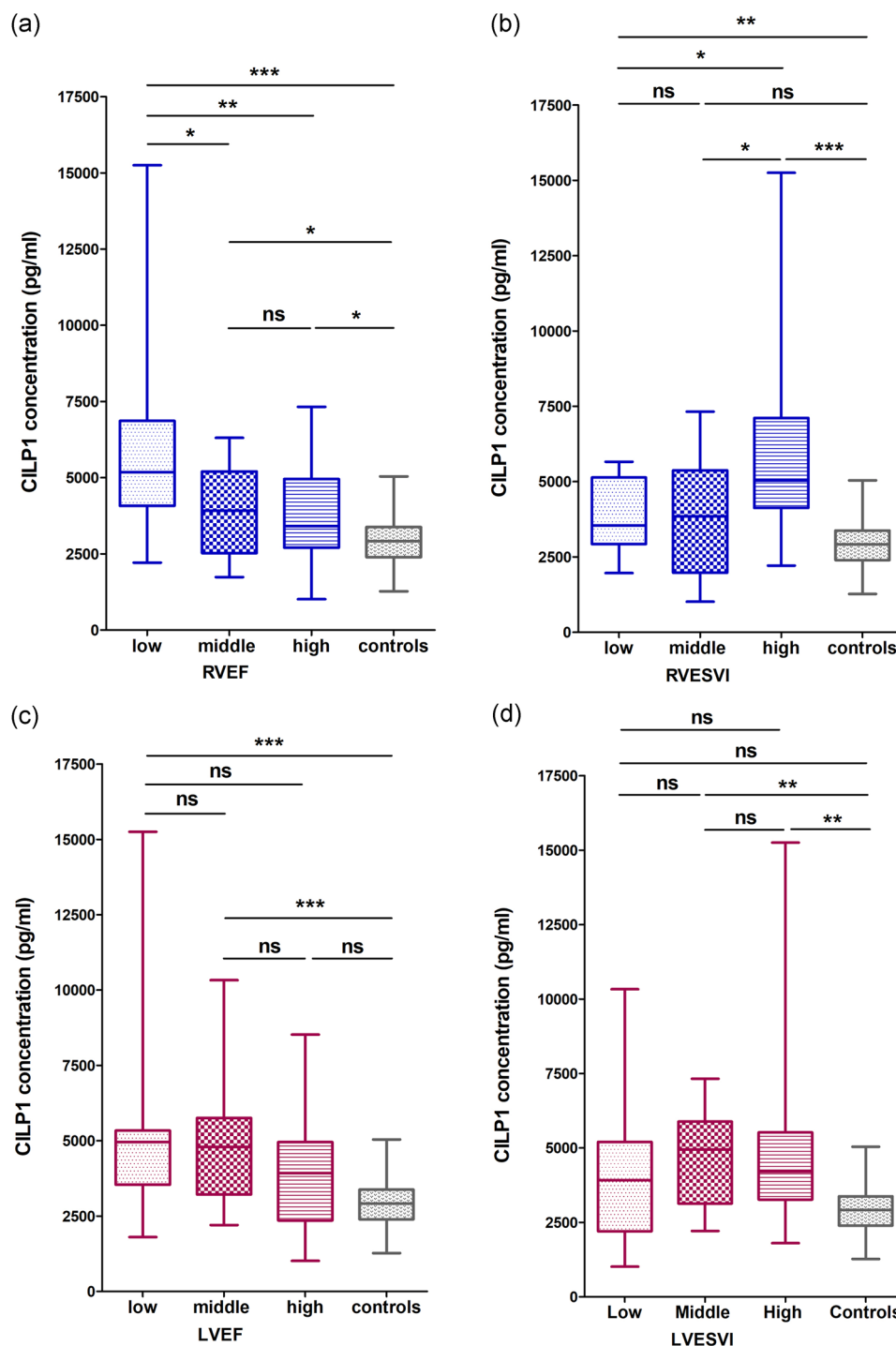
The present study is the first to analyze the association of CILP1 plasma concentrations with CMR parameters of RV and LV remodeling in patients with ICM.

The main findings of the study are: (1) ICM is associated with higher CILP1 levels than controls; (2) increased CILP1 concentrations in ICM are associated with systolic RV dysfunction, RV dilation, and higher NT-proBNP levels; (3) CILP1 concentrations in ICM were not associated with LV dysfunction or dilation; (4) RVEF is an independent predictor of high CILP1 concentrations ( $\geq 3545$  pg/ml).

Existing evidence shows that RV dysfunction is associated with a worse prognosis in patients with left heart failure and specifically in ICM. RVEF is one of the most important prognostic parameters of systolic RV function and decreased RVEF was an independent predictor of mortality in several studies with ICM patients.<sup>2–5</sup> In a study of 147 consecutive patients with prior myocardial infarction RVEF < 40% was an independent predictor of mortality.<sup>5</sup> Additionally, in a large CMR cohort of 7131 patients with known or suspected cardiovascular disease, RVEF < 40% was an independent predictor of heart failure admission, need for transplantation/LV-assisted device, or death.<sup>19</sup> Increased RVESVI as a parameter of RV dilation was also associated with higher mortality in a CMR cohort of patients with LV heart failure.<sup>20</sup>

In our study, we used CMR imaging, which is the current standard for measuring LV and RV dimensions

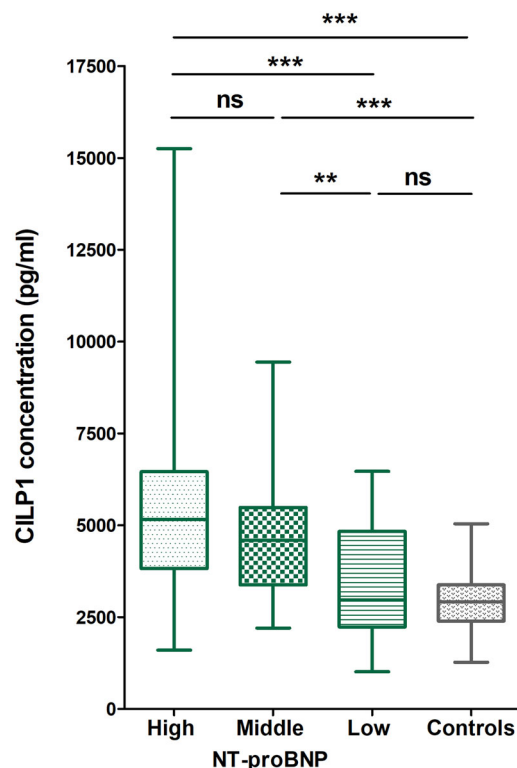




**FIGURE 1** Box and scatter plots showing CILP1 levels according to (a) RVEF tertiles (low: <45%; middle: 45–54%, high >54%), (b) RVESVI tertiles (low: <32 ml/m<sup>2</sup>; middle: 32–43 ml/m<sup>2</sup>; high: >43 ml/m<sup>2</sup>), (c) LVEF tertiles (low: <35%; middle: 35–52%; high: >52%) and (d) LVESVI tertiles (low: <39 ml/m<sup>2</sup>; middle: 39–66 ml/m<sup>2</sup>; high: >66 ml/m<sup>2</sup>) in patients with ischemic cardiomyopathy. Boxes represent median with IQR. ns, not significant, \* $p < 0.05$ , \*\* $p < 0.01$ , and \*\*\* $p < 0.001$ . CILP1, cartilage intermediate layer protein 1; IQR, interquartile range; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume index

and function with good reliability and reproducibility,<sup>6,21</sup> to analyze associations of CILP1 concentrations with prognostic parameters of LV and RV remodeling in patients with ICM and healthy controls. The baseline

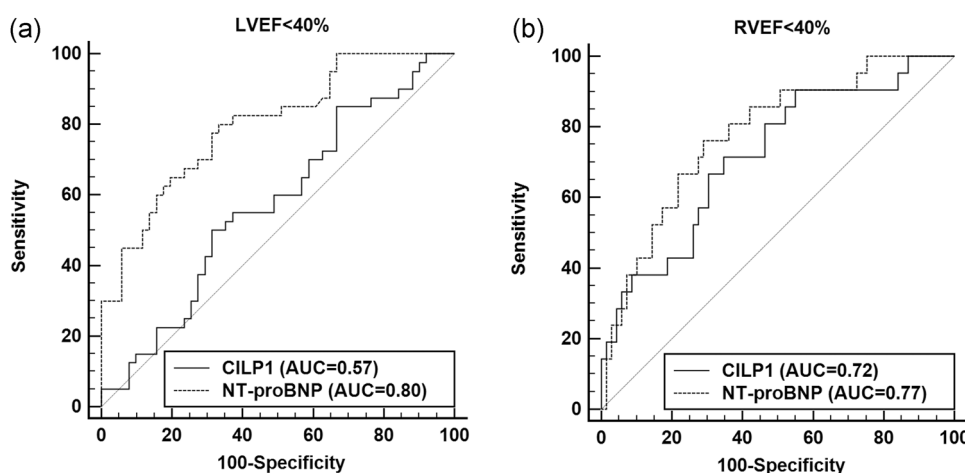
characteristics of the two groups showed that half of all ICM patients had LVEF < 40% and a third had RVEF < 40%, whereas all controls had normal systolic LV and RV function.



**FIGURE 2** Box and scatter plots showing CILP1 levels according to NT-proBNP tertiles (low: <465 pg/ml; middle: 465–1800 pg/ml; high: >1800 pg/ml) in patients with ischemic cardiomyopathy. Boxes represent median with IQR. ns, not significant,  $**p < 0.01$ , and  $***p < 0.001$ . CILP1, cartilage intermediate layer protein 1; IQR, interquartile range; NT-proBNP, N-terminal pro-brain natriuretic peptide

CILP1 is a myocardial matricellular protein that was identified as an inhibitor of transforming growth factor- $\beta$  (TGF- $\beta$ ) signaling<sup>10</sup> and its expression is induced by TGF- $\beta$ .<sup>22</sup> CILP1 gene encodes a precursor protein that is cleaved in an N-terminal fragment containing a TGF $\beta$ 1-binding WSXW motif and a C-terminal fragment, homologous to nucleotide pyrophosphohydrolase.<sup>23</sup> Full-length CILP1 protein is mainly produced by cardiac fibroblasts and undergoes intracellular or extracellular cleavage by furin proteases.<sup>10,12,13,24</sup>

CILP1 concentrations in our ICM cohort were markedly higher than in controls. This corresponds to previous findings that show higher CILP1 concentrations in 142 patients with dilated cardiac myopathy (DCM), left ventricular hypertrophy, and PH as compared to healthy controls.<sup>13</sup> In contrast, a recent study by Park et al.<sup>24</sup> showed significantly reduced CILP1 levels in 22 patients with ischemic heart failure as compared to 23 healthy individuals. This study used an antibody that spans the cleavage site to measure the serum concentration of full-length precursor CILP1 protein. The antibody used in our CILP1 studies binds to a sequence within the N-terminal fragment. Therefore, our assay measured plasma concentrations of precursor CILP1 protein and N-terminal fragment. Precursor protein and N-terminal fragment are secreted in the ECM and can both bind TGF- $\beta$ 1 and thus inhibit profibrotic TGF $\beta$  signaling, which is known to induce collagen expression in infarcted areas and promote myofibroblast transdifferentiation.<sup>12</sup> Furin, the protease that cleaves precursor CILP1, was also shown to play an essential role in the



**FIGURE 3** Receiver-operating characteristics curve showing the predictive power of CILP1 and NT-proBNP for (a) LVEF < 40% and (b) RVEF < 40% % in patients with ischemic cardiomyopathy. AUC, area under the curve; CILP1, cartilage intermediate layer protein 1; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; RVEF, right ventricular ejection fraction

**TABLE 2** Clinical characteristics of patients grouped according to CILP1 cut-off value

Variable	CILP1 $\geq$ 3545 pg/ml ( <i>n</i> = 60)	CILP1 < 3545 pg/ml ( <i>n</i> = 38)	<i>p</i> Value
Age (years), median (IQR)	68 (63–76)	65 (54–77)	0.23
Female sex, <i>n</i> (%)	15 (25)	8 (21)	0.65
BMI (kg/m <sup>2</sup> ), median (IQR)	2.00 (1.83–2.16)	2.01 (1.89–2.17)	0.39
BSA (m <sup>2</sup> ), median (IQR)	27 (24–30)	27 (26–30)	0.48
Cardiovascular risk factors			
Hypertension, <i>n</i> (%)	48 (80)	32 (84)	0.6
Diabetes, <i>n</i> (%)	21 (35)	9 (24)	0.24
Dyslipidemia, <i>n</i> (%)	43 (72)	27 (71)	0.95
Smoker, <i>n</i> (%)	18 (31)	11 (29)	0.8
Clinical history			
Chronic pulmonary disease, <i>n</i> (%)	9 (15)	6 (16)	0.89
CAD, <i>n</i> (%)	60 (100)	38 (100)	1
Prior MI, <i>n</i> (%)	51 (86)	32 (84)	0.76
Prior PCI, <i>n</i> (%)	45 (75)	28 (76)	0.94
Prior CABG, <i>n</i> (%)	12 (20)	9 (24)	0.7
Atrial fibrillation, <i>n</i> (%)	0 (0)	1 (3)	0.03
Prior stroke/TIA, <i>n</i> (%)	23 (40)	7 (18)	0.25
NYHA $\geq$ 3, <i>n</i> (%)	18 (34)	9 (36)	0.86
Echocardiographic findings			
LVEF (%), median (IQR), <i>n</i> = 73	36 (30–50)	48 (40–55)	0.07
IVSd (mm), median (IQR), <i>n</i> = 65	11 (9–12)	11 (9–12)	0.98
LVPWd (mm), median (IQR), <i>n</i> = 63	10 (8–12)	11 (9–12)	0.34
RVEDd (mm), median (IQR), <i>n</i> = 65	39 (30–44)	38 (28–45)	0.91
TAPSE (mm), mean ( $\pm$ SD), <i>n</i> = 70	19 (16–22)	18 (17–23)	0.82
PASP (mmHg), mean ( $\pm$ SD), <i>n</i> = 51	33 (31–36)	33 (31–39)	0.69
MRI findings			
HF (1/min), median (IQR)	68 (60–76)	67 (61–72)	0.1
LVEF (%), median (IQR)	43 (28–55)	46 (33–60)	0.39
LVEF < 40%, <i>n</i> (%)	28 (47)	13 (35)	0.24
LVESV (ml), median (IQR)	109 (70–180)	98 (67–140)	0.25
LVESVI (ml/m <sup>2</sup> ), median (IQR)	53 (35–88)	50 (34–65)	0.22
LVEDV (ml), median (IQR)	200 (144–260)	184 (158–217)	0.39
LVEDVI (ml/m <sup>2</sup> ), median (IQR)	96 (73–130)	87 (78–104)	0.26
RVEF (%), median (IQR)	47 (30–54)	54 (50–60)	<0.001
RVEF < 40%, <i>n</i> (%)	20 (34)	2 (6)	0.001
RVESV (ml), median (IQR)	79 (64–110)	70 (49–86)	0.02
RVESVI (ml/m <sup>2</sup> ), median (IQR)	41 (33–53)	32 (26–39)	0.002
RVEDV (ml), median (IQR)	154 (124–173)	157 (117–182)	0.77
RVEDVI (ml/m <sup>2</sup> ), median (IQR)	76 (68–87)	74 (62–84)	0.2



**TABLE 2** (Continued)

Variable	CILP1 $\geq$ 3545 pg/ml ( <i>n</i> = 60)	CILP1 < 3545 pg/ml ( <i>n</i> = 38)	<i>p</i> Value
Biomarker			
Creatinine (mmol/L), median (IQR)	1.00 (0.83–1.45)	0.84 (0.71–0.95)	0.003
eGFR (ml/min/1.73.m <sup>2</sup> ), median (IQR)	70 (47–97)	97 (81–114)	0.002
NT-proBNP (pg/ml), median (IQR)	1499 (647–4285)	430 (181–1258)	<0.001

Abbreviations: BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CILP1, cartilage intermediate layer protein 1; eGFR, estimated glomerular filtration rate; HF, heart frequency; IQR, interquartile range; IVSd, diastolic interventricular septum thickness; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVPWd, diastolic left ventricular posterior wall thickness; MRI, magnetic resonance imaging; MI, myocardial infarction; n.a., not available; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PASP pulmonary arterial systolic pressure; PCI, percutaneous coronary intervention; TAPSE, tricuspid annular plane systolic excursion; RVEF, right ventricular ejection fraction; RVEDd, right ventricular end-diastolic diameter; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume, RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index.

**TABLE 3** Multivariable analysis of parameters as predictors of (a) high serum CILP concentration and (b) RVEF < 40%

(a)	<i>p</i> Value	Odds ratio	95% CI
NT-proBNP	0.95	1	1
eGFR	0.06	0.98	0.97–1.002
RVEF	0.01	0.94	0.90–0.98
Atrial fibrillation	0.27	2.51	0.6–6.19
(b)	<i>p</i> Value	Odds ratio	95% CI
CILP1	0.001	2.01	1.32–3.07
NT-proBNP	0.99	1	1
LVEF	<0.001	0.87	0.81–0.94

Abbreviations: CI, confidence interval; CILP1, cartilage intermediate layer protein 1; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; RVEF, right ventricular ejection fraction.

activation of TGF $\beta$ 1 and membrane-type 1 matrix metalloproteinase.<sup>25</sup> Interestingly, furin expression was induced by TGF- $\beta$ 1<sup>25</sup> and was also increased after myocardial infarction in rodents.<sup>26</sup> These findings suggest that CILP1, TGF- $\beta$ 1, and furin may form a functional feedback loop that plays an important role in pathological ECM remodeling. An increased furin expression under the activation of pathological TGF- $\beta$  signaling could also cause an increased cleavage of CILP1 precursor protein. This could explain the differences in CILP1 concentrations between our analyses and the data presented by Park et al.

The most important finding of our study is the ability of CILP1 to detect RV dysfunction and dilation in patients with ICM. Low RVEF and high RVESVI were associated with higher CILP1 concentrations. CILP1 was also an independent predictor of RVEF < 40% and high CILP1 levels were associated with higher NT-proBNP levels,

which are established and prognostically relevant biomarkers of maladaptive RV remodeling.<sup>27–29</sup> However, natriuretic peptides like NT-proBNP are not specific biomarkers and can be elevated in almost any heart disease with hemodynamic effect. In our analysis, high NT-proBNP levels were associated with both low LVEF and RVEF in tertile analysis as well as in subgroup analysis and NT-proBNP was a good predictor of LVEF < 40% and RVEF < 40%. Consequently, our analysis confirms that NT-proBNP is a reliable biomarker of heart failure, but it cannot differentiate between LV and RV failure.

Interestingly, there were no associations of CILP1 levels with any parameters of LV remodeling in the entire cohort and in the subgroups with LVEF  $\leq$  50% or RVEF > 50%.

The results of our analysis correspond to the findings of a previous study that demonstrated higher CILP1 concentrations in PH patients with maladaptive RV function (systolic RV dysfunction and RV dilation) than in patients with DCM or severe aortic stenosis and LV hypertrophy without PH and RV remodeling.<sup>13</sup> The hypothesis of higher CILP1 levels in RV remodeling than in LV remodeling is further supported by experimental data revealing a 26-fold upregulation of CILP1 in mice with pulmonary artery constriction and only a fivefold upregulation in mice subjected to transverse aortic constriction, despite a similar degree of outflow tract obstruction.<sup>30</sup>

In summary, experimental and clinical findings show that maladaptive RV remodeling leads to a significant increase in CILP1 levels both in participants with and without concomitant LV remodeling. Conversely, there are no associations between CILP1 levels and LV parameters. Hence, CILP1 could serve as a biomarker of maladaptive RV remodeling in different cardiopulmonary pathologies.

There are several possible explanations for these findings. CILP1 is a matricellular protein that is secreted by myofibroblasts in the ECM of the heart.<sup>10</sup>

Matricellular proteins act locally in the ECM by regulating different signaling pathways.<sup>31</sup> Therefore, there might be a differential expression and upregulation of CILP1 signaling in pathological RV remodeling as compared to LV remodeling.

Several animal and human studies show that CILP1 levels are associated with myocardial fibrosis,<sup>10,24</sup> suggesting that CILP1 and TGF- $\beta$  may form a functional feedback loop. Thus, CILP1 upregulation could prevent excess fibrosis by inhibiting TGF- $\beta$  signaling.

A review of several histological studies in patients with PH showed only a moderate RV fibrosis under chronic RV pressure overload (up to 9.6%),<sup>32</sup> whereas another study revealed a much more pronounced LV fibrosis under chronic LV pressure overload in patients with severe aortic stenosis (up to 29.5%).<sup>33</sup> In a study of patients with hypertrophic cardiomyopathy, a pathology associated with pronounced myocardial fibrosis, subjects with RV and LV hypertrophy showed less RV fibrosis than LV fibrosis in biopsies and CMR.<sup>34</sup> This evidence shows that under pathological remodeling, there could be more fibrosis in the LV than in the RV.

A stronger CILP1 expression in pathological RV remodeling as compared to LV remodeling could therefore lead to a stronger inhibition of TGF $\beta$  signaling and less fibrosis in the RV, which provides a possible explanation for the higher CILP1 levels in ICM patients with pathological RV remodeling. This hypothesis is supported by previous findings showing higher CILP1 concentrations in PH patients with maladaptive RV remodeling as compared to patients with DCM or LV hypertrophy without RV dysfunction.<sup>13</sup>

This is a single-center study of observational nature. The sample size was rather small, which could limit the validity of our analyses. There were significant differences in terms of age and sex between the ICM and control group, which could influence the results of our analysis.

## CONCLUSION

Our analysis demonstrates the potential role of CILP1 as a biomarker of maladaptive RV remodeling in ICM that is associated with prognostic CMR parameters of RV dimensions and systolic function. Consequently, CILP1 could improve the diagnostic and prognostic stratification in patients with ICM.

## AUTHOR CONTRIBUTIONS

Stanislav Keranov designed the trial, cleaned and analyzed the data, and drafted and revised the paper. He is the guarantor. Leili Jafari performed biomarker measurements and revised the draft paper. Saskia Haen collected additional

echocardiographic data and revised the draft paper. Julia Vietheer monitored MRI measurements and data collection and revised the draft paper. Steffen Kriechbaum monitored data collection and revised the draft paper. Oliver Dörr monitored data collection and revised the draft paper. Christoph Liebetrau monitored data collection and revised the draft paper. Christian Troidl monitored data collection and revised the draft paper. Wiebke Rutsatz monitored MRI measurements and revised the draft paper. Andreas Rieth monitored data collection and revised the draft paper. Christian W. Hamm monitored data collection and revised the draft paper. Andreas Rolf designed the trial, monitored statistical analysis and data collection, and revised the draft paper. Till Keller designed the trial, monitored statistical analysis and data collection, and revised the draft paper.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## ETHICS STATEMENT

The BioCVI registry is approved by the local ethics committee, participation was voluntary, and all patients gave written informed consent.

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## SUPPORTING INFORMATION

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