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Tissue inhibitor of metalloproteinase (TIMP)-1 predicts failure of recovery of ejection fraction in acute heart failure with reduced ejection fraction

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ABSTRACT

Background Heart failure (HF) with improved ejection fraction (HFimpEF) is a recently identified phenotype of HF, which had better cardiovascular outcomes compared with persistent HF with reduced ejection fraction (HFrEF). The present study aimed to investigate the predictive value of tissue inhibitor of metalloproteinase (TIMP)-1 and matrix metalloproteinases-9 (MMP-9) in the recovery of left ventricular ejection fraction (LVEF).

Methods Subjects who presented with acute decompensated HF and reduced LVEF of ≤40% were eligible for this study. HFimpEF was defined by a follow-up LVEF >40% and a ≥10% improvement in LVEF. Overnight fasting N-terminal pro-brain natriuretic peptide (NT-proBNP), MMP-9 and TIMP-1 were measured within 24 hours before discharge. The study participants were followed for up to 5 years.

Results Among a total of 91 participants (70.1±16.2 years, baseline LVEF 28.9±7.6%), 19 (20.8%) of them had HFimpEF and 72 (79.2%) had persistent HFrEF at 6 months. The receiver operating characteristic curve analyses showed the area under curve measures for TIMP-1, MMP-9 and NT-proBNP in the prediction of HFimpEF were 0.69, 0.52 and 0.65, respectively. TIMP-1 was negatively correlated with HFimpEF as continuous variables (OR per 1-SD and 95% CI 0.99 (0.98 to 1.00)) and categorical variables (cut-off value 200.68 ng/mL, OR and 95% CI 0.16 (0.05 to 0.54)) after adjustment of confounding factors. During a mean follow-up duration 34.8 months, patients with HFimpEF will have better long-term survival than those with persistent HFrEF.

Conclusions In subjects with decompensated HFrEF, TIMP-1, but not MMP-9 was associated with the reverse remodelling in LVEF. In addition, patients with HFimpEF would have better long-term survival.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Heart failure (HF) with improved ejection fraction (HFimpEF) has been identified as a phenotype with better cardiovascular outcomes compared to persistent HF with reduced ejection fraction (HFrEF). However, the biomarkers that predict HFimpEF are not well understood.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that tissue inhibitor of metalloproteinase (TIMP)-1 is an independent predictor of HFimpEF, whereas matrix metalloproteinases-9 is not. Additionally, patients with HFimpEF show better long-term survival compared to those with persistent HFrEF.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings highlight the importance of TIMP-1 as a biomarker for predicting HFimpEF, which could guide personalised treatment strategies for HF patients and be a potential focus for future research on therapeutic interventions.

INTRODUCTION

The ACC/AHA guidelines in 2022 have classified the phenotypes of heart failure (HF) not only by the baseline measures of left ventricular ejection fraction (LVEF) but also by the trajectory of LVEF.[1] HF with improved LVEF (HFimpEF) as a new category is suggested to follow and continue the treatments of HF with reduced LVEF (HFrEF).[1] Florea *et al* have demonstrated in the Val-HeFT trial of 5010 HFrEF subjects that the HFimpEF subjects had better 3-year survival, compared with those with persistent HFrEF.[2] In another cohort of 361 patients with idiopathic dilated cardiomyopathy, Merlo *et al* found that HFimpEF was an independent predictor of less mortality, ventricular arrhythmia and heart transplant events.[3] Female gender, higher body mass index (BMI), shorter HF duration, non-ischaemic aetiology, absence of left bundle branch block (LBBB) and low N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were associated with HFimpEF.[4 5] In addition to the clinical characteristics, Lupón *et al* further

illustrated a low serum ST2 levels was related to the development of HFimpEF.[6] However, little was known about the biomarkers and LV reverse remodelling in HFimpEF.

The matrix metalloproteinases (MMPs) were a family of proteinases that facilitated the degradation of the extracellular matrix and regulated the fibrosis and remodelling of the myocardium.[7] Tissue inhibitor of metalloproteinase (TIMP) was a protein that regulated the activity of MMPs and may be upregulated in myocardial infarction, LV hypertrophy and HF.[7 8] The upregulation of TIMP-1 in HFrEF was associated with ventricular remodelling and poor prognosis. Frantz *et al* have demonstrated in a cohort of 249 chronic HF subjects that high TIMP-1 was associated with larger left ventricular end-diastolic volume (LV EDV) and higher 2-year mortality.[9] In the post-hoc analysis of PARADIGM-HF, baseline and 8 months of TIMP-1 were both positively associated with cardiovascular death and HF hospitalisation.[10] However, there was still knowledge gap of TIMP-1 and MMPs in the prediction of LV reverse remodelling. The present study therefore investigated the roles of TIMP-1 and MMPs on the trajectory of LVEF among hospitalised patients with HFrEF.

METHODS

Subjects and the study protocol

The present study enrolled consecutive patients hospitalised for decompensated HF that fulfilled the Framingham criteria of HF.[11] Patients with acute coronary syndrome, significant valvular heart diseases, severe infection with a SOFA score of ≥2, haematopoietic diseases or active malignancy were excluded. After the standard care, the study participants would undergo echocardiographic studies before discharge.[12] Subjects with LVEF of ≤40% were then recruited in this analysis.

The study participants would undergo repeated echocardiographic studies 6 months after discharge. HFimpEF was defined with the second measure of LVEF >40% and a ≥10% increase in LVEF. The others were considered to have persistent HFrEF.

Echocardiography and laboratory data

Echocardiography was conducted according to the recommendations of the American Society of Echocardiography.[13] LVEF, LV EDV and left ventricular end-systolic volume (LV ESV) were measured by using biplane Simpson's method.[13] Left ventricular internal diameter at end-diastole and end-systole, posterior wall and interventricular septum thickness in diastole, left ventricular mass index and left atrial volume index were obtained. Pulmonary artery systolic pressure and tricuspid annular plane systolic excursion were also measured with continuous wave doppler and M-mode echocardiogram.

A 15cc fasting blood sample was obtained before the echocardiographic study. Serum TIMP-1 (R&D Systems, Abingdon, UK), MMP-9 (R&D Systems, Abingdon, UK) and NT-proBNP (Roche Diagnostics, Basel, Switzerland) were measured. Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease formula with adjustment for Chinese patients.

Follow-up

The study participants were followed in the outpatient clinics every 3 months and through telephone consultation to identify the adverse clinical events, including HF hospitalisation, myocardial infarction and mortality. Patients were followed for up to 5 years.

Statistical analysis

Continuous variables were demonstrated as mean±SD and categorical variables were reported as absolute number and percentage. For the comparisons between groups, the Student's t-test was used in continuous variables and the χ^2 test in categorical variables. The changes of the repeated echocardiographic measures were evaluated by using paired sample t-test. The receiver operating characteristic (ROC) analysis was performed to evaluate the predictive value of the biomarkers and HFimpEF. Youden index was used to determine the cut-off values of the biomarkers. The univariate and multivariate binary logistic regression analyses were performed to assess the associations between the biomarkers and HFimpEF. All the analyses were conducted with IBM/SPSS V.22.0 (SPSS, Chicago, IL, USA) and R-statistical software (http://www.r-project.org/). All the tests performed were two-sided, and p value <0.05 was considered statistically significant.

RESULTS

A total of 91 HFrEF patients (70.1±16.2 years, 85.7% men) with a baseline LVEF of 28.9±7.6% were enrolled in this study. At 6-month echocardiographic follow-up, 19 (20.8%) subjects experienced recovery in LVEF, and 72 (79.2%) have persistent HFrEF. The baseline characteristics showed no difference between two groups in age, gender distribution, comorbidities, left ventricular structures and functions, and medications (table 1). The serum TIMP-1 and NT-proBNP were significantly higher in the subjects with persistent HFrEF compared with HFimpEF (figure 1). The serum MMP-9 level was similar between the groups. There were significant reductions in LV ESV and LV EDV, and improvement of LVEF at 6-month follow-up in HFimpEF subjects but not in those with persistent HFrEF (table 2). In addition, the HFimpEF subjects had significantly better 5-year survival rate than the persistent HFrEF subjects (figure 2a). But the HF hospitalisation rate and composite outcome of HF hospitalisation and mortality were similar between the two groups (figure 2b,c). The 1-year landmark analysis of the composite outcome of HF hospitalisation and mortality were significantly lower in the HFimpEF subjects (figure 2c).

The ROC analysis showed that the area under curve (AUC) of TIMP-1, MMP-9 and NT-proBNP were 0.690, 0.519 and 0.651, respectively (figure 3). The cut-off value

Table 1 Baseline characteristics of the study population, n=91

	All (n=91)	HFimpEF (n=19)	Persistent HFrEF (n=72)	P value
Age (years)	70.1±16.2	70.3±17.4	70.0±16.0	0.943
Male gender, n (%)	78 (85.7)	17 (89.5)	61 (84.7)	0.599
Vital signs, on admission				
SBP, mm Hg	136.2±28.4	140.7±36.7	135.0±26.0	0.527
DBP, mm Hg	81.9±19.6	87.2±22.1	80.4±18.9	0.186
Pulse rate, bpm	93.5±19.7	100.0±20.0	91.8±19.5	0.111
Comorbidity, n (%)				
Hypertension	65 (71.4)	15 (78.9)	50 (69.4)	0.415
Diabetes mellitus	41 (45.1)	10 (52.6)	31 (43.1)	0.456
Previous ACS	29 (31.9)	7 (36.8)	22 (30.6)	0.601
Coronary artery disease	64 (70.3)	13 (68.4)	51 (70.8)	0.838
COPD	14 (15.4)	2 (10.5)	12 (16.7)	0.509
LBBB	9 (9.9)	1 (5.3)	8 (11.1)	0.448
Echocardiography				
LVEF (%)	28.9±7.6	30.0±8.1	28.6±7.5	0.469
LV EDV (mL)	147.31±53.09	148.90±47.79	156.10±59.50	0.942
LV ESV (mL)	103.93±44.50	102.97±41.49	112.95±49.53	0.916
E/A ratio	1.56±0.94	1.24±0.80	1.65±0.96	0.100
LAVi (mL/m^2)	14.36±3.39	13.88±4.32	14.56±3.01	0.602
LVIDd (mm)	29.4±28.8	34.3±28.5	28.0±29.0	0.408
LVIDs (mm)	24.4±24.1	27.7±23.4	23.5±24.4	0.509
IVSd (mm)	10.3±2.2	10.4±2.5	10.3±2.1	0.911
LV mass index	150.0±37.4	149.7±30.1	150.2±39.3	0.942
PASP (mm Hg)	44.7±20.5	40.5±15.3	46.5±22.4	0.449
TAPSE (cm)	2.15±1.69	1.83±0.48	2.27±1.97	0.491
Haemogram and biochemistry, on admission				
Haemoglobin (g/L)	122.6±21.9	126.4±21.5	121.6±22.0	0.402
eGFR (mL/min/1.73m^2)	55.0±25.5	59.6±29.5	53.7±24.4	0.376
Sodium (mEq/L)	138.6±4.2	138.0±3.7	138.8±4.3	0.430
Potassium (mEq/L)	4.00±0.67	3.89±0.57	4.04±0.69	0.386
Ln NT-proBNP (pg/mL), n=45*	8.33±1.96	7.23±3.46	8.69±0.98	0.030
TIMP-1 (ng/dL)	229.3±89.6	239.6±95.7	189.9±44.3	0.031
MMP-9 (ng/dL)	264.5±247.1	271.3±265.0	238.9±165.8	0.614
Medications, n (%)				
Beta-blocker	56 (61.5)	14 (73.7)	42 (58.3)	0.221
RAS blockade	69 (75.8)	14 (73.7)	55 (76.4)	0.807
Digoxin	17 (18.7)	5 (26.3)	12 (16.7)	0.337
Spironolactone	56 (61.5)	14 (73.7)	42 (58.3)	0.221

*Geometric means and SD.
ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; E/A ratio, the ratio of early to late trans-mitral flow velocity; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HFimpEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IVSd, interventricular septal diameter at end diastole; LAVi, the left atrium volume index; LBBB, left bundle branch block; LV, left ventricular; LVIDd, left ventricular internal diameter at end diastole; LVIDs, left ventricular internal diameter at end systole; NT-proBNP, N-terminal pro-brain natriuretic peptide; PASP, pulmonary arterial systolic pressure; RAS blockade, renin-angiotensin system blockade; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion.

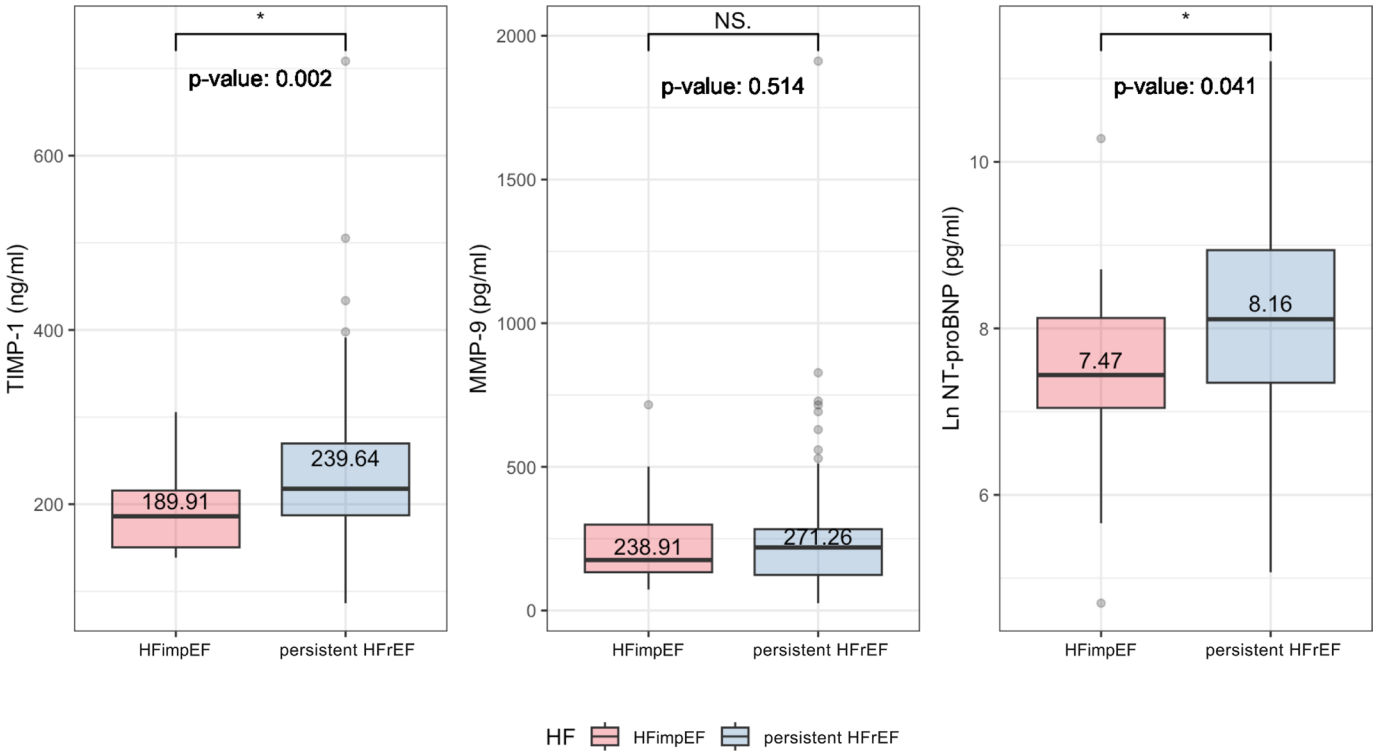

Figure 1 The difference of the biomarkers in HFimpEF and persistent HFrEF patients TIMP-1 and NT-proBNP were significantly higher in persistent HFrEF compared with HFimpEF, while MMP-9 was similar between these two phenotypes of HF. HF, heart failure; HFimpEF, HF with improved ejection fraction; HFrEF, HF with reduced ejection fraction; MMP-9, matrix metalloproteinases-9; NT-proBNP, N-terminal pro-brain natriuretic peptide; TIMP-1, tissue inhibitor of metalloproteinase-1.

of 200.68 ng/mL for TIMP-1 was used to stratify the study population, resulting in a sensitivity of 0.694 and a specificity of 0.684. Subjects with low TIMP-1 would have significant improvements in LVEF mainly due to the remodelled LV ESV, compared with those with high TIMP-1 (table 2). In the univariate logistic regression analysis, only TIMP-1 and NT-proBNP but not MMP-9 or TIMP-1/MMP-9 ratio were associated with HFimpEF (table 3). The correlation with HFimpEF was not observed in MMP-9, or TIMP-1/MMP-9 ratio. After adjusting for age, gender, LVEF, history of MI and presence of LBBB, TIMP-1 remained an independent predictor of HFimpEF. (TIMP-1 as a continuous variable, OR per 1-SD of 8.96 and 95% CIs 0.990 (0.979 to 1.000); TIMP-1 as a categorical variable: 0.158 (0.046 to 0.544).)

DISCUSSION

The present study has clearly demonstrated that subjects with HFimpEF had better long-term survival compared with those with persistent HFrEF. Serum TIMP-1 level was associated with the recovery of LVEF among the decompensated patients with HFrEF. Moreover, lower

Table 2 Follow-up echocardiographic parameters in acute heart failure with reduced ejection fraction

	Persistent HFrEF			HFimpEF		
	Pre-discharge	6-month follow-up	P value*	Pre-discharge	6-month follow-up	P value*
LV EDV (mL)	156.10±59.50	156.48±60.69	0.946	148.90±47.79	124.74±48.87	0.029
LV ESV (mL)	112.95±49.53	108.07±44.41	0.279	102.97±41.49	64.41±30.03	<0.001
LVEF (%)	28.98±7.67	31.10±8.06	0.095	30.02±8.11	49.70±6.38	<0.001
	TIMP-1 ≥200.68 mg/mL			**TIMP-1 <200.68 mg/mL**		
LV EDV (mL)	151.17±51.85	148.27±51.32	0.681	156.65±61.30	144.91±67.73	0.124
LV ESV (mL)	107.79±44.06	99.63±43.63	0.126	112.44±51.26	88.69±46.96	0.002
LVEF (%)	29.24±7.90	33.57±10.71	0.024	29.36±7.71	40.63±11.29	<0.001

*Paired-samples t-test.
HFimpEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV EDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LV ESV, left ventricular end-systolic volume; TIMP-1, tissue inhibitor of metalloproteinase-1.

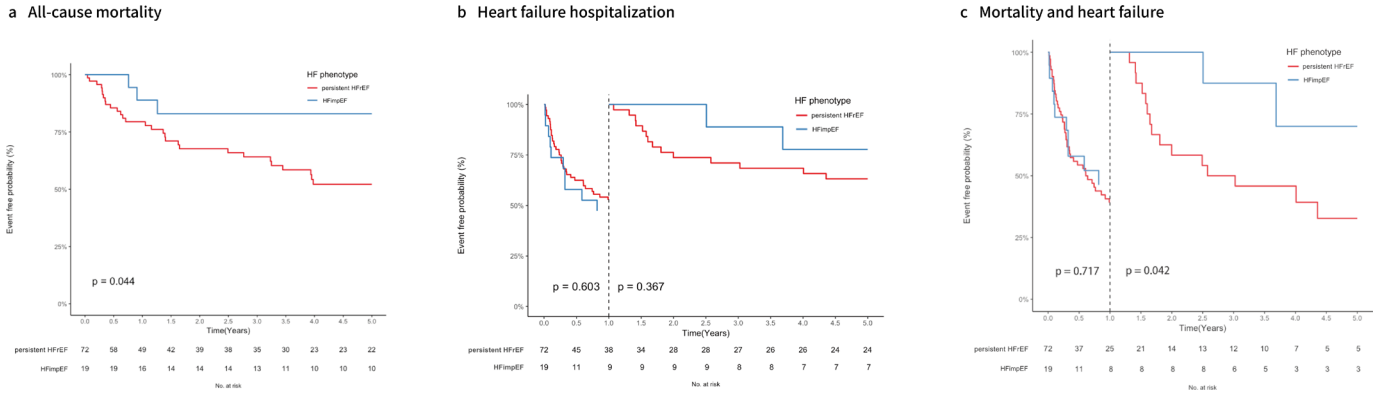

Figure 2 Kaplan-Meier analysis of prognosis of HFimpEF and persistent HFrEF patients. The Kaplan-Meier survival curve analysis of 5-year all-cause mortality (a), 1-year landmark analysis of heart failure hospitalisation (b) and 1-year landmark analysis of mortality and heart failure hospitalisation (c) stratified by HFimpEF and persistent HFrEF patients. HF, heart failure; HFimpEF, HF with improved ejection fraction; HFrEF, HF with reduced ejection fraction.

serum TIMP-1 levels were related to a greater reduction in LV ESV but not LV EDV and improvement of LVEF. TIMP-1, but not MMP-9, was an independent predictor of HFimpEF in acute HF (AHF) patients, regardless of age, gender, LVEF, history of acute myocardial infarction or presence of LBBB.

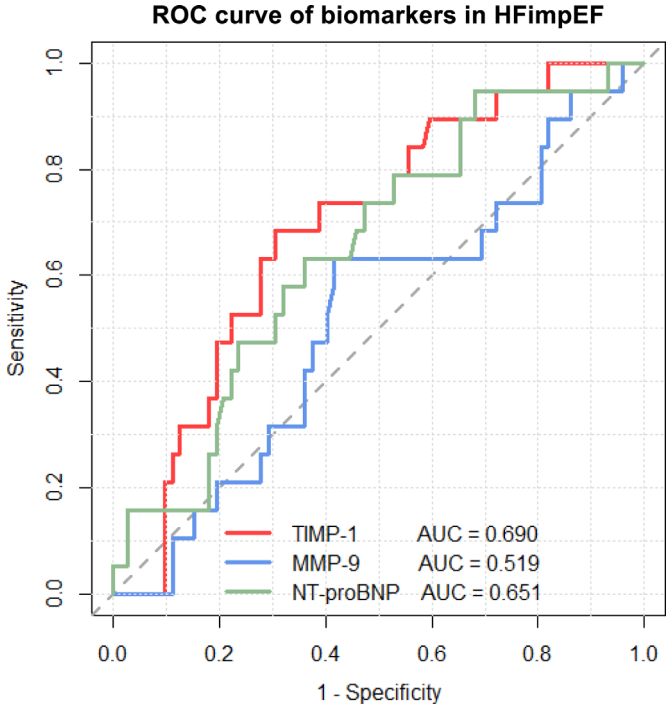

Figure 3 ROC analysis of biomarkers in the prediction of HFimpEF. The area under the ROC curve for recovery of ejection fraction of TIMP-1, MMP-9 and NT-proBNP were 0.690, 0.519 and 0.651, respectively. The combination model of TIMP-1 and NT-proBNP showed an AUC of 0.748. The optimal cut-off value of TIMP-1 according to Youden index was 200.68 ng/mL. AUC, area under curve; HFimpEF, heart failure with improved ejection fraction; MMP-9, matrix metalloproteinases-9; NT-proBNP, N-terminal pro-brain natriuretic peptide; ROC, receiver operating characteristic; TIMP-1, tissue inhibitor of metalloproteinase-1.

Prognosis of HFimpEF

HFimpEF was a rebalance, the adaptive and the compensatory status of the previous HFrEF. In Val-HeFT trial with 5010 HFrEF subjects, the incidence of improvement of LVEF from <35% to >40% was 9.1%.[2] The baseline neurohormonal profiles and 3-year survival of subjects with the improvement of LVEF were better than persistent HFrEF. In a meta-analysis of nine studies of HFrEF, the prevalence of improvement of LVEF was 22.64% and it also showed lower mortality and adverse cardiac events in the subjects with the improvement of LVEF.[14] The incidence of HFimpEF was 20.8%, which was similar to the previous studies. The recovery of ejection fraction derived from both the reduction in LV EDV and ESV with a greater extent in ESV. The finding was consistent with the result of the study by Park *et al* with 5625 HFrEF patients that the recovery of ejection fraction derived mainly from the improvement in ESV.[15] The 5-year all-cause mortality was significantly lower in HFimpEF subjects than in HFrEF. However, the composite of HF hospitalisation and cardiovascular-related death were similar. The result was mainly driven by the high incidence of HF hospitalisation rate (HFrEF vs HFimpEF: 68.1% vs 63.2%) in both groups. The result suggested that though the ejection fraction was phenotypically recovered, the histological irreversible insult may persist and lead to a similar outcome to HFrEF but not HFpEF.

Risk factors associated with reverse remodelling of HFrEF

Reverse remodelling of HFrEF was a multifactorial process and involved various underlying mechanisms, such as myocardial ischaemia, inflammation, oxidative stress and neurohormonal activation. Recent studies have demonstrated the risk factors associated with reverse remodelling. Lupón *et al* demonstrated in a cohort with 304 HFrEF subjects that lower serum solute ST2 level, non-ischaemic aetiology, absence of LBBB, HF duration <12 months, lower LVEF and beta-blocker treatment were independent predictors of reverse remodelling in HFrEF.[6] Kramer *et al* showed in a meta-analysis with

Table 3 Univariate and multivariate logistic regression analysis of heart failure with improved ejection fraction in acute heart failure patients

	Univariate		Multivariate (TIMP-1, per 1-SD=8.96)		Multivariate (TIMP-1, cut-off value 200.68 ng/mL)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
TIMP-1	0.989 (0.980 to 0.999)	0.027	0.990 (0.979 to 1.000)	0.047		
TIMP-1(cat)*	0.203 (0.068 to 0.604)	0.004			0.158 (0.046 to 0.544)	0.003
MMP-9	0.999 (0.997 to 1.002)	0.613				
TIMP-1/MMP-9 ratio	0.684 (0.368 to 1.273)	0.231				
NT-proBNP†	0.643 (0.420 to 0.987)	0.043	0.649 (0.399 to 1.056)	0.082	0.577 (0.348 to 0.958)	0.577

Adjust age, gender, LVEF, AMI, LBBB, NT-proBNP in the multivariate analysis.
*TIMP-1(cat): the group with higher TIMP-1 versus those with lower TIMP-1, cut-off point 200.68 by Youden's index.
†Log transformation of NT-proBNP.
AMI, acute myocardial infarction; DM, diabetes mellitus; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MMP-9, matrix metalloproteinases-9; NT-proBNP, N-terminal pro-brain natriuretic peptide; TIMP-1, tissue inhibitor of metalloproteinases-1.

88 randomised control trial of HFrEF that using beta-blocker, renin-angiotensin system blockade, mineralocorticoid receptor antagonist, cardiac resynchronisation therapy (CRT) and etanercept had an absolute effect on reduction of EDV, ESV and improvement of LVEF.[16] Lilli *et al* revealed in a study with 334 HFrEF subjects undergoing CRT implantation that the female gender was associated with a greater reduction in LV ESV compared with male subjects.[17] In addition, comorbidities also influenced the reverse remodelling of LV. In a study with 184 HFrEF subjects, higher BMI were positively correlated with HFimpEF.[5] Neurohormone and biomarkers could also be potential predictors of reverse remodelling of LV. Florea *et al* demonstrated in the analysis of Val-HeFT study with 5010 HFrEF subjects that the subjects with HFimpEF had favourable neurohormone and biomarker profiles such as lower norepinephrine, renin activity, endothelin, NT-proBNP, GDF-15 and sST2 compared with the subjects with HFrEF.[2] It is important to note that while these factors have been associated with reverse remodelling, they do not guarantee that a patient will experience this process. Treatment and management of HFrEF should be tailored to each patient's individual needs and should involve a multidisciplinary team approach.

MMPs and TIMP-1 in the remodelling of HFrEF

MMPs were found to be upregulated in deteriorating HF.[18] MMP may be stimulated by inflammation response, cause the subsequent elevation of pro-fibrotic cytokines such as TGF-β, degrade extracellular proteins, led to the loss of the normal fibrillar collagen network and cause fibrosis of myocardium.[7 19] Spinale *et al* demonstrated the preceding increase of left ventricle MMP protein levels and zymographic activities followed by decreasing of contractility in a pacing LV-failure animal model.[20] Yan *et al* also showed a positive correlation of plasma MMP-9 with LV ESV.[21] The smaller proportional increase in plasma MMP-9 level was associated with improvement in LVEF after accounting for age, gender and medications.[21] In a study of hypertensive HF animal model, treatment with MMP inhibitors was associated with decreasing myocardial MMP-2 and MMP-9 activity and reduction of LV dilatation.[22] In addition, higher MMP-9 was associated with increasing severity of symptoms of HF, and was an independent predictor of worsening of HF in a study of 173 chronic HF subjects.[23] However, in the present study, the serum MMP-9 level was similar between HFimpEF subjects and persistent HFrEF subjects. In addition, the MMP-9 was not an independent predictor for HFimpEF. Though activation of MMP-9 was associated with fibrosis and disarrangement of collagen network, MMP-9 was not the determinant of recovery of EF and reverse remodelling of myocardium, which may be a multifactorial process that needed further investigation.

TIMP-1 regulated the activity of MMP and was also upregulated in HF subjects.[18] TIMP-1 was a profibrotic biomarker that mediated cardiac fibrosis during HF.[10] Takawale *et al* demonstrated the reduction of cardiac fibrosis in the TIMP-1 knock-out mice cardiac pressure overload model.[24] In addition, the higher plasma TIMP-1 was associated with poor functional capacity, higher mortality and adverse cardiovascular events in HFrEF.[9] In the study of Morishita *et al*, higher plasma level of TIMP-1 was observed in the chronic HF subjects with worse New York Functional Class.[23] Frantz *et al* showed TIMP-1 was an independent predictor of all-cause mortality in Wurzburg Heart Failure Registry.[9] Zile *et al* demonstrated that plasma TIMP-1 was not only higher in the HFrEF subjects compared with healthy control subjects, but also associated with higher cardiovascular death and HF hospitalisation.[10]

The present study demonstrated the low serum TIMP-1 level subjects had a greater reduction in LV ESV and improvement in LVEF. In addition, serum TIMP-1 level was higher in the HFimpEF subjects, and the predictive value of TIMP-1 of HFimpEF after adjustment of age, gender, LVEF, myocardial infarction and the presence of LBBB. The higher TIMP-1 represented the more severe inflammation response and more severe pro-fibrotic

status that needed to be regulated by increasing the expression of TIMP-1. The study result was consistent with the previous study of CRT, which also showed TIMP-1 was negatively correlated with the reverse remodelling of LV ESV and was an independent predictor of the responder of CRT.[25] In addition, the cut-off value for prediction of responder was 248 ng/mL, which was similar to the cut-off value 200.68 ng/mL in the prediction of HFimpEF in the present study. In the extended study of PARADIGM-HF, the HFrEF subjects under the treatment of sacubitril/valsartan had a significantly greater lowering of TIMP-1 compared with those treated with enalapril after 8 months of follow-up.[10] The results suggested that TIMP-1 mediated the homeostasis of ECM and the fibrosis of the myocardium, that could be possibly reversed or suppressed by currently proposed guideline-direct therapy. Thus, TIMP-1 could be a predictor of HFimpEF and a potential marker for treatment responder of HF.

Difference in predictive value between the biomarkers

The predictive value of TIMP-1 and MMPs was inconsistent in the previous studies. Tolosana *et al* revealed that plasma TIMP-1 level, but not MMP-2, was correlated with the reverse remodelling of LV, response to CRT and cardiovascular mortality in a cohort of CRT-treated HFrEF subjects.[25] Yan *et al* showed that increasing plasma MMP-9 level, but not TIMP-1, correlated with improvement of LVEF in HFrEF subjects.[21] In the present study, we demonstrated TIMP-1 to be an independent predictor of reverse remodelling of LV.

The difference in the predictive value of TIMP-1 and MMP-9 in reverse remodelling may be due to the underlying mechanism. TIMP-1 in the remodelling of LV was considered associated with the suppression of the activity of MMPs. However, TIMP-1 also mediated cardiac fibrosis with an MMP-independent pathway. Takawale *et al* demonstrated in the LV pressure-overload animal model that TIMP-1 would activate an MMP-independent pathway of Smad 2/3 and β-catenin of cardiac fibroblast and precipitated cardiac fibrosis.[24] In vitro study of fibroblast cell showed that TIMP-1 could stimulate proliferation of fibroblast through activation of the p-Akt pathway, which was also an MMP-independent pathway.[26] However, further studies were needed to determine whether the difference in the predicting value of TIMP-1 and MMP-9 in reverse remodelling of LV derived from these previously proposed pathways.

NT-proBNP was a neurohormonal marker for LV distension. Daubert *et al* demonstrated in GUIDE-IT randomised control trial that decreasing NT-proBNP to <1000 pg/mL at 1-year follow-up was associated with better survival, fewer adverse cardiovascular events, as well as reverse remodelling of LV.[27] In a cohort with 44 new-onset symptomatic, dilated cardiomyopathy patients with LVEF <45%, BNP at 3 months was an independent predictor of reverse remodelling at 1 year.[28] The present study showed that subjects with HFimpEF may have higher NT-proBNP. The combination model of TIMP-1 and NT-proBNP increased AUC in the prediction of HFimpEF to 0.748, which was better than TIMP-1 alone. In addition, the combination of NT-proBNP and TIMP-1 had an even better prediction of HFimpEF after accounting for confounders. The result suggested that NT-proBNP as the surrogate of congestion of LV, and TIMP-1 as the surrogate for profibrotic response and extent of inflammation could predict reverse remodelling and recovery of EF through different mechanisms and provide higher predictive value when combined.

Study limitations

There were several limitations of the present study. First, this was a retrospective observational study, which was prone to be influenced by selection bias at enrolment. We have adjusted all possible confounders to minimise the influences. Second, the relatively small size of the study population may lead to concerns about underpowering. However, the result remained significant even in such small study populations. Last but not the least, the study was conducted before the publication of landmark trials of some present guideline-direct treatments.[29 30] We could not evaluate the influence of current guideline-direct treatments on TIMP-1 in the prediction of HFimpEF.

CONCLUSION

In the AHF patients with reduced ejection fraction, HFimpEF had a better long-term survival rate. The subjects with lower serum TIMP-1 may have a greater reduction of LV ESV and improvement of LVEF at 6-month follow-up. In addition, the serum TIMP-1, but not MMP-9, was negatively correlated to the recovery of EF and was an independent predictor of HFimpEF after accounting for confounding factors.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the study was conducted according to the principles in the Declaration of Helsinki and was approved by Institutional Review Board of Taipei Veterans General Hospital (ID: IRB-TPEVGH No: 2016-01-001BC). Participants gave informed consent to participate in the study before taking part.

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