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Original article

Association of plasma thioredoxin-1 with renal tubular damage and cardiac prognosis in patients with chronic heart failure

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ABSTRACT

Background: Thioredoxin-1 (Trx-1) is an abundant 12.5 kDa redox protein expressed in almost all eukaryotic cells that protect against the development of heart failure and kidney dysfunction. Plasma Trx-1 levels are considered as a reliable marker for oxidative stress. However, it remains to be determined whether plasma Trx-1 levels can predict cardiac prognosis in patients with chronic heart failure (CHF).

Methods and results: We measured plasma Trx-1 levels and urinary β_2-microglobulin–creatinine ratio (UBCR), a marker for renal tubular damage, in 156 consecutive patients with CHF and 17 control subjects. The patients were prospectively followed for a median follow-up period of 627 days and 46 cardiac events were observed. The patients with cardiac events had significantly higher plasma Trx-1 levels and UBCR levels than the cardiac event-free patients. Multivariate Cox proportional hazard analysis revealed that an elevated Trx-1 level was independently associated with poor outcome in patients with CHF after adjustment for confounding factors (hazard ratio, 1.74; 95% confidence interval, 1.33–2.29; $p < 0.0001$). UBCR was increased with higher plasma Trx-1 levels. Kaplan–Meier analysis demonstrated that the highest Trx-1 tertile was associated with the highest risk of cardiac events.

Conclusion: Plasma Trx-1 level was associated with renal tubular damage and cardiac prognosis, suggesting that it could be a useful marker to identify patients at high risk for comorbid heart failure and renal tubular damage.

Introduction

Heart failure is a major health problem with high mortality that continues to increase in prevalence [1–4]. The development of heart failure is closely associated with progressive left ventricular remodeling in response to oxidative stress [5]. The major source of excessive oxidative stress in heart failure is considered to be increased intracellular levels of reactive oxygen species (ROS) [6].

Thioredoxin-1 (Trx-1) is an abundant 12.5 kDa cytosolic protein expressed in almost all eukaryotic cells and plays an important role in redox signaling. Trx-1 contains a dithiol/disulfide motif in the redox-active site and serves as an ROS scavenger [7,8]. Circulating Trx-1 was reported to be closely associated with systemic oxidative stress [9,10] and was used as a reliable oxidative stress marker. However, it is not known whether plasma Trx-1 is a useful prognostic marker of chronic heart failure (CHF).

Cardio-renal interaction was evaluated because kidney dysfunction is indicative of extremely poor prognosis in patients with CHF [11,12]. Notably, oxidative stress is a common pathophysiological factor in the development of cardiac and kidney dysfunction, and experimental studies have demonstrated that Trx-1 inhibits oxidative stress in both heart and kidney tissue [13,14]. We previously reported that renal tubular damage, as well as glomerular damage, is a risk factor for poor prognosis in patients with CHF [15]. Renal tubular cells are located in the renal medulla, which is affected by hypoxia. Thus, we hypothesized that plasma Trx-1 was associated with CHF-induced renal tubular damage.

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The purpose of the present study was to examine whether Trx-1 could predict cardiac prognosis in patients with CHF.

Methods

Study subjects

This was a prospective study of 156 consecutive patients who were admitted to our hospital for diagnosis or treatment of CHF. Seventeen age-matched control subjects who had no heart disease were also entered. The diagnoses of CHF were made by two cardiologists who used the generally accepted Framingham criteria, including a history of dyspnea and symptomatic exercise intolerance, signs of pulmonary congestion, peripheral edema, and radiological or echocardiographic evidence of left ventricular enlargement or dysfunction.

Transthoracic echocardiography was performed by physicians who were blinded to the biochemical data. The diagnoses of hypertension, diabetes mellitus, and hyperlipidemia were established on the basis of the patient's medical records or history of currently or previously received medical therapy. Ten patients were excluded from the study due to acute coronary syndrome within 3 months preceding the admission, active hepatic disease, pulmonary disease, or malignant disease. Demographic and clinical data including age, gender, New York Heart Association (NYHA) functional class, and medications at discharge were collected from hospital medical records and patient interviews.

Biochemical assays

Venous blood and urine samples were obtained in the early morning within 24 h of admission. Plasma Trx-1 was measured with human thioredoxin-1 enzyme-linked immunosorbent assay (ELISA) kits (Japan Institute for the Control of Aging, Nikken Seil Co., Ltd., Shizuoka, Japan). Brain natriuretic peptide (BNP) concentrations were measured using a commercially available specific radioimmunoassay for human BNP (Shiono RIA BNP assay kit, Shionogi Co., Ltd., Tokyo, Japan) [16]. The estimated glomerular filtration rate (GFR) was calculated using the modification of diet in renal disease (MDRD) equation with the Japanese coefficient as previously reported [17]. We quantitatively measured urinary albumin by immunoturbidimetry in a single spot urine specimen collected in the early morning. Urinary albumin levels were corrected for urinary creatinine in a single manner to urinary microalbumin–creatinine ratio (UACR). Urinary β_2-microglobulin concentration to creatinine ratio (UBCR), a marker for renal tubular damage, was determined by the latex agglutination method (BML, Inc., Tokyo, Japan) [18]. N-acetyl-β-D-glucosaminidase (NAG), a marker of early renal tubular damage, was measured in single spot urine specimens. Because BNP, UACR, UBCR, NAG, and Trx-1 were not normally distributed, we performed all analyses using log-transformed values.

End-points and follow-up

The patients were prospectively followed for a median period of 627 days (interquartile range, 406–896 days). All the patients were followed by telephone interview or medical record review twice a year for 1250 days. The end points were cardiac death (defined as death from progressive heart failure, acute coronary syndrome, or sudden cardiac death) and progressive heart failure requiring rehospitalization. Sudden cardiac death was defined as death without definite premonitory symptoms or signs and was established by the attending physician.

The study was approved by the institutional ethics committee, and all the patients provided informed consent.

Statistics

All values are expressed as the mean ± standard deviation (SD). We employed *t*-tests, chi-square tests, and linear analysis to compare continuous and categorical variables, respectively. Kruskal–Wallis test was used to compare Trx-1 with NYHA functional class. A Cox proportional hazard analysis was performed to determine independent predictors for cardiac events. Significant predictors selected in the univariate analysis were entered into the multivariate analysis. The receiver operating characteristics curve of Trx-1 was constructed to determine the area under the curve (AUC), sensitivity, and specificity. The AUC for cardiac events was calculated by the trapezoidal rule. Proportionality in the Cox model was evaluated with log-minus-log survival plots. A cardiac event-free curve was constructed according to the Kaplan–Meier method and compared using a log-rank test. A p-value <0.05 was considered statistically significant. Statistical analyses were performed with a standard program package (JMP version 8; SAS Institute Inc., Cary, NC, USA).

Results

Baseline patient characteristics

The subjects' baseline characteristics are presented in Table 1. There were 96 patients with NYHA functional class II and 60 patients with class III or IV. Hypertension, diabetes mellitus, and hyperlipidemia were identified in 101 (65%), 43 (28%), and 53

Table 1
Clinical characteristics of patients with chronic heart failure and control subjects.

Variables	Control $n=17$	All patients $n=156$	p value
Age, years	69 ± 5	72 ± 10	0.1638
Gender (men/women)	7/10	100/56	0.0646
NYHA functional class (II/III, IV)		96/60	
Hypertension, *n* (%)	12 (71%)	101 (65%)	0.4240
Diabetes mellitus, *n* (%)	2 (17%)	43 (28%)	0.2778
Hyperlipidemia, *n* (%)	6 (35%)	53 (34%)	0.9685
Etiology			
Ischemic heart disease, *n* (%)		41 (26%)	
Nonischemic heart disease, *n* (%)		115 (74%)	
Blood examination			
Log_{10} BNP (pg/mL)	1.4 ± 0.3	2.6 ± 0.5	<0.0001
Log_{10} Trx-1 (ng/mL)	1.7 ± 0.4	2.1 ± 0.8	0.0445
Kidney function			
eGFR (mL/min/1.73 m^2)	72 ± 8	67 ± 26	0.5411
Log_{10} UACR (mg/g)	1.2 ± 0.9	1.5 ± 0.6	0.1823
Log_{10} UBCR (μg/g)	1.6 ± 0.7	2.2 ± 0.9	0.0445
Log_{10} NAG (U/g)	0.77 ± 0.12	1.01 ± 0.29	0.0139
Echocardiography			
LVEDD (mm)	47 ± 6	56 ± 10	0.0155
LVEF (%)	70 ± 6	49 ± 17	0.0004
Medication			
ACEIs and/or ARBs, *n* (%)		117 (75%)	
β-Blockers, *n* (%)		117 (75%)	
Statin, *n* (%)		61 (39%)	
Aldosterone blockers, *n* (%)		44 (28%)	
Loop diuretics, *n* (%)		104 (67%)	

Data are expressed as mean ± SD, number (percentage).
ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II recepter blockers; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; NAG, N-acetyl-β-D-glucosaminidase; NYHA, New York Heart Association; Trx-1, thioredoxin 1; UACR, urinary albumin to creatinine ratio; UBCR, urinary β_2-microglobulin to creatinine ratio.

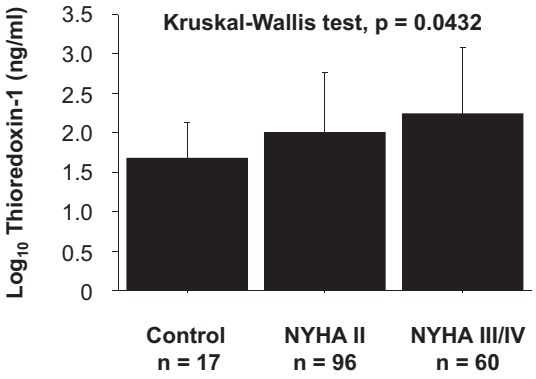

Fig. 1. The association between Trx-1 and NYHA functional class. Trx-1 was increased with advancing NYHA functional class (Kruskal–Wallis test, $p = 0.0432$). NYHA, New York Heart Association; Trx-1, thioredoxin-1.

(34%) patients with CHF, respectively. Heart failure etiologies were identified as ischemic heart disease (IHD) in 41 (26%) patients and non-IHD in 115 (74%) patients. The mean $\log_{10}$ Trx-1 value was 2.1 ± 0.8 ng/mL. Plasma Trx-1 levels increased with advancing NYHA functional class (Fig. 1).

Association of plasma Trx-1 and renal tubular damage markers

To investigate the relationship between plasma Trx-1 and renal tubular damage, we preformed simple linear analysis. There was significant correlation between plasma Trx-1 and renal tubular damage markers (UBCR: $r = 0.169$, $p = 0.0347$; NAG: $r = 0.172$, $p = 0.0324$, respectively). Also, $\log_{10}$ UACR correlated to plasma Trx-1 (UACR: $r = 0.178$, $p = 0.0267$). On the other hand, there was no significant correlation between plasma Trx-1 and other parameters including age, $\log_{10}$ BNP, estimated glomerular filtration rate (eGFR), left ventricular end diastolic diameter, and left ventricular ejection fraction.

Comparison of clinical characteristics between patients with and without cardiac events

There were 46 cardiac events (29% of patients) during the follow-up period, including eight cardiac deaths and 38 re-hospitalizations for worsening heart failure. The causes of cardiac death were worsening CHF in five patients, ventricular fibrillation in one patient, acute coronary syndrome in one patient, and sudden cardiac death in one patient.

As shown in Table 2, patients who experienced cardiac events were in a more severe NYHA functional class than those who did not. Patients with cardiac events showed a higher prevalence of IHD; higher $\log_{10}$ BNP, $\log_{10}$ Trx-1, $\log_{10}$ UACR, $\log_{10}$ UBCR, and $\log_{10}$ NAG; and lower eGFR compared to those without. Patients with cardiac events took more β-blockers and diuretics than those who did not experience events. There were no significant differences between the two groups in age, gender, prevalence rates of hypertension, diabetes mellitus, and hyperlipidemia, and echocardiographic parameters.

Trx-1 and clinical outcomes

We performed univariate and multivariate Cox proportional hazard regression analyses to identify risk factors for cardiac events (Table 3). In the univariate analysis, Trx-1 was significantly associated with cardiac events. Furthermore, NYHA functional class, diabetes mellitus, eGFR, $\log_{10}$ BNP, $\log_{10}$ UACR, $\log_{10}$ UBCR, and $\log_{10}$ NAG were significantly related to cardiac event occurrence. The multivariate analysis revealed that Trx-1 was an independent

Table 2
Comparisons of clinical characteristics between patients with and without cardiac events.

Variables	Event free $n = 110$	Cardiac event $n = 46$	p value
Age, years	71 ± 10	73 ± 11	0.4058
Gender (men/women)	67/43	33/13	0.1985
NYHA functional class (II/III, IV)	76/34	20/26	0.0027
Hypertension, *n* (%)	70 (64%)	31 (67%)	0.6544
Diabetes mellitus, *n* (%)	27 (25%)	16 (35%)	0.1920
Hyperlipidemia, *n* (%)	35 (32%)	18 (39%)	0.3792
Etiology			0.0058
Ischemic heart disease, *n* (%)	22 (20%)	19 (41%)	
Non-ischemic heart disease, *n* (%)	88 (80%)	27 (59%)	
Blood examination			
$\log_{10}$ BNP (pg/mL)	2.5 ± 0.4	2.7 ± 0.5	0.0206
$\log_{10}$ Trx-1 (ng/mL)	1.9 ± 0.7	2.6 ± 0.8	<0.0001
Kidney function			
eGFR (mL/min/1.73 m^2)	70 ± 22	60 ± 32	0.0270
$\log_{10}$ UACR (mg/g)	1.3 ± 0.6	1.8 ± 0.6	0.0001
$\log_{10}$ UBCR (μg/g)	1.9 ± 0.7	2.8 ± 1.0	<0.0001
$\log_{10}$ NAG (U/g)	0.97 ± 0.28	1.14 ± 0.32	0.0006
Echocardiography			
LVEDD (mm)	55 ± 9	57 ± 10	0.5949
LVEF (%)	50 ± 18	48 ± 16	0.6385
Medication			
ACEIs and/or ARBs, *n* (%)	83 (76%)	34 (74%)	0.8393
β-Blockers, *n* (%)	77 (70%)	40 (87%)	0.0257
Statin, *n* (%)	42 (38%)	19 (41%)	0.7155
Aldosterone blockers, *n* (%)	32 (29%)	12 (26%)	0.7038
Loop diuretics, *n* (%)	65 (59%)	39 (85%)	0.0019

Data are expressed as mean ± SD, number (percentage).
ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II recepter blockers; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; NAG, N-acetyl-β-D-glucosaminidase; NYHA, New York Heart Association; Trx-1, thioredoxin 1; UACR, urinary albumin to creatinine ratio; UBCR, urinary β_2-microglobulin to creatinine ratio.

Table 3
Univariate and multivariate Cox proportional hazard analysis of predicting cardiac events in patients with chronic heart failure.

Variables	Hazard ratio	95% confidence interval	p value
Univariate analysis			
Age (per 1 year increase)	1.02	0.98–1.06	0.2794
Gender (woman vs. man)	0.63	0.33–1.23	0.1786
NYHA functional class (III, IV vs. II)	2.66	1.46–4.85	0.0015
Hypertension	1.31	0.68–2.51	0.4187
Diabetes mellitus	1.95	1.06–3.57	0.0320
Hyperlipidemia	1.36	0.74–2.49	0.3246
$\log_{10}$ BNP (per 1-SD increase)	1.51	1.07–4.54	0.0173
$\log_{10}$ Trx-1 (per 1-SD increase)	1.69	1.36–2.10	<0.0001
eGFR (per 1-SD increase)	0.64	0.47–0.93	0.0157
$\log_{10}$ UACR (per 1-SD increase)	1.90	1.44–2.52	<0.0001
$\log_{10}$ UBCR (per 1-SD increase)	2.68	2.02–3.56	<0.0001
$\log_{10}$ NAG (per 1-SD increase)	1.81	1.32–2.47	0.0002
LVEDD (per 1 SD increase)	1.16	0.84–1.61	0.3607
LVEF (per 1 SD increase)	0.89	0.84–1.51	0.4246
Multivariate analysis			
NYHA functional class (III, IV vs. II)	1.85	0.98–3.47	0.0574
eGFR (per 1 SD increase)	0.77	0.53–1.08	0.1432
$\log_{10}$ BNP (per 1 SD increase)	1.17	0.80–1.70	0.4154
$\log_{10}$ Trx-1 (per 1 SD increase)	1.74	1.33–2.29	<0.0001

BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; NAG, N-acetyl-β-D-glucosaminidase; NYHA, New York Heart Association; Trx-1, thioredoxin 1; UACR, urinary albumin to creatinine ratio; UBCR, urinary β_2-microglobulin to creatinine ratio.

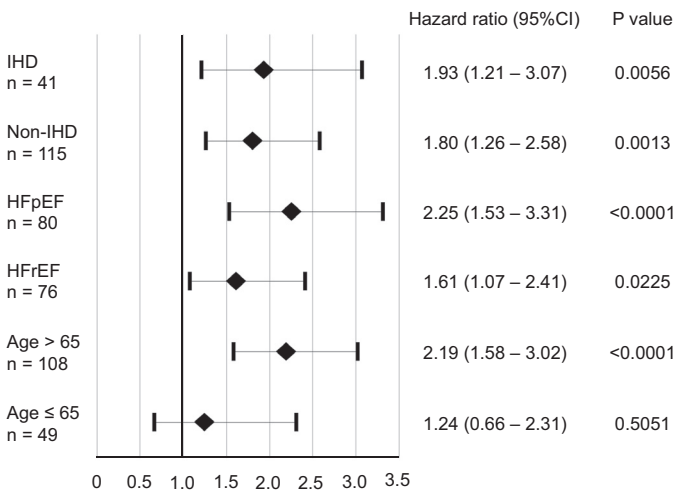

Fig. 2. Univariate analysis of plasma Trx-1 to predict future cardiac events in the settings of IHD, non-IHD, heart failure with preserved ejection fraction (HFpEF: left ventricular ejection fraction > 50%), heart failure with reduced ejection fraction (HFrEF: left ventricular ejection fraction ≤ 50%), elderly age (>65 years old), and young age (≤65 years old). Plasma Trx-1 was significantly related to cardiac events in patients with IHD, non-IHD, HFpEF, HFrEF, and elderly age. On the other hand, plasma Trx-1 was not related to future cardiac events in young patients with CHF. Trx-1, thioredoxin-1; IHD, ischemic heart disease.

predictor for cardiac events after adjustment of NYHA functional class, eGFR, and $\log_{10}$ BNP (Trx-1, hazard ratio 1.74; 95% confidence interval, 1.33–2.29, $p < 0.0001$) (Table 3).

Subgroups analyses were performed in the setting of IHD, non-IHD, HF with reduced ejection fraction (HFrEF: left ventricular ejection fraction ≤ 50%), HF with preserved ejection fraction (HFpEF: left ventricular ejection fraction > 50%), elderly age (>65 years old), and young age (≤65 years old). Patients with IHD had higher plasma Trx-1 than non-IHD patients (2.3 ± 0.9 vs. 2.0 ± 0.8, $p = 0.0211$). On the other hand, there was no significant difference in plasma Trx-1 level between HFrEF and HFpEF and elderly age and young age. As shown in Fig. 2, plasma Trx-1 was significantly related to future cardiac events in patients with IHD, non-IHD, HFpEF, HFrEF, and elderly age. However, plasma Trx-1 was not associated with cardiac events in young patients with CHF.

Trx-1 and risk stratification

The patients were divided into three groups based on the Trx-1 levels: first tertile (≤1.6 ng/mL), $n = 52$; second tertile (1.6–2.4 ng/mL), $n = 52$; and third tertile (>2.4 ng/mL), $n = 52$. Third tertile patients exhibited a higher mean $\log_{10}$ UBCR compared to those in the first tertile (Fig. 3A). Similarly, second and third tertile patients showed higher levels of $\log_{10}$ NAG than those in the first tertile (Fig. 3B). On the other hand, there were no significant differences in glomerular damage as assessed by $\log_{10}$ UACR and eGFR (Fig. 3C and D). The risk ratios were 1.0, 2.9, and 5.2 for the first to third tertiles, respectively (Fig. 4A). Kaplan–Meier analysis demonstrated that the third tertile had the highest rate of cardiac events among the three groups (Fig. 4B).

Comparison of Trx-1 and BNP prognostic values

The receiver operating characteristics curve was constructed to determine the optimal cut-off value, sensitivity, and specificity of Trx-1. The AUC, sensitivity, and specificity were 0.74, 70%, and 71%, respectively. Interestingly, the AUC of Trx-1 was larger than that of BNP (Fig. 5).

Combination of plasma Trx-1 and UBCR

We divided all CHF patients into three groups based on the abnormal level of UBCR (UBCR ≥ 300 μg/g) and abnormal level of plasma Trx-1 ($\log_{10}$ Trx-1 > 2.2 ng/mL): (1) normal group, $n = 70$; (2) high Trx-1 or high UBCR group, $n = 61$; and (3) high Trx-1 + high UBCR group, $n = 25$. The Kaplan–Meier analysis demonstrated that high Trx-1 + high UBCR group had the greatest risk in patients with CHF (Fig. 6).

Discussion

The results of this study yielded several novel findings: (1) Trx-1 was increased with advancing HF; (2) patients with cardiac events had higher levels of plasma Trx-1 than those without it; (3) multivariate Cox proportional hazard analysis demonstrated that Trx-1 was an independent predictor of cardiac events; (4) patients with elevated plasma Trx-1 had higher levels of renal tubular damage markers, such as $\log_{10}$ UBCR and $\log_{10}$ NAG; and (5) the Kaplan–Meier analysis revealed that the risk of cardiac events was greatest in the highest Trx-1 tertile.

Oxidative stress and heart failure

Oxidative stress has garnered much interest for its role in CHF development [19,20]. It is associated with apoptosis or necrosis in cardiomyocytes, extracellular matrix remodeling, and contractile and endothelial dysfunction with resultant cardiac remodeling in the failing heart [21]. Trx-1 was reported to reduce intracellular ROS generation and subsequent cardiac cell loss in response to ROS [22]. Experimental studies indicated that Trx-1 overexpression protects against cardiac cell apoptosis and is associated with good cardiac function in animal models of HF [14,23]. Trx-1 is reportedly rapidly released into the circulation from the damaged cardiomyocytes [24,25], and is increased with advancing CHF severity [9]. Here we showed for the first time that plasma Trx-1 is an independent predictor of future cardiac events. The receiver operating characteristics curve analysis demonstrated that the AUC of plasma Trx-1 was greater than that of BNP. Multivariate Cox proportional hazard regression analysis revealed that plasma Trx-1 was an independent predictor of future cardiac events, even after adjustment for BNP in patients with CHF. Therefore, plasma Trx-1 can provide additional clinical information to BNP values and may serve as a marker to stratify CHF patients by risk.

Oxidative stress in CHF and kidney dysfunction

Oxidative stress is a pathophysiological process fundamental to both HF and kidney dysfunction. It was reported that urinary 8-hydroxy-2′-deoxyguanosine, also a useful oxidative stress marker, is not related to eGFR [26]. Similarly, there was no significant difference in glomerular damage markers, such as eGFR and $\log_{10}$ UACR, in patients in different Trx-1 tertiles. However, patients with high Trx-1 values had higher UBCR and NAG values, suggesting that renal tubular damage was associated with oxidative stress in patients with CHF. We previously reported that renal tubular damage is also a risk factor for cardiac events in patients with CHF as well as glomerular damage [15,27,28]. Renal tubular damage was recognized as a final common pathway for end-stage renal dysfunction [29,30]. Thus, patients with high plasma Trx-1 may have poor cardiac prognosis due to the development of kidney dysfunction in addition to severe HF. Furthermore, high Trx-1 + high UBCR group had the greatest risk in patients with CHF, suggesting that combined measurement of plasma Trx-1 and UBCR could be a highly reliable evaluation for risk-stratifying patients with CHF. Our results clearly

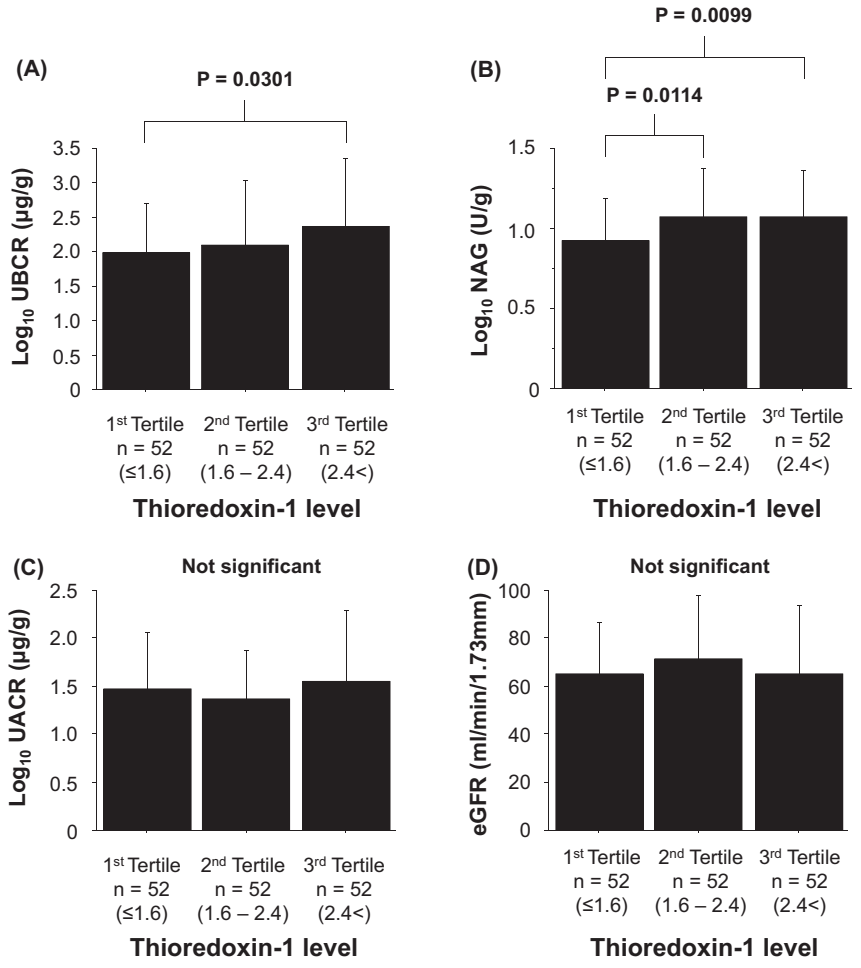

Fig. 3. (A) The association between plasma Trx-1 and $\log_{10}$ UBCR. The third tertile of plasma Trx-1 had higher levels of $\log_{10}$ UBCR compared to the first tertile ($p = 0.0301$). (B) The association between plasma Trx-1 and $\log_{10}$ NAG. The second and third tertiles of plasma Trx-1 had higher levels of $\log_{10}$ NAG than the first tertile (third tertile, $p = 0.0099$; second tertile, $p = 0.0114$). (C) The association between plasma Trx-1 and $\log_{10}$ UACR. (D) The association between plasma Trx-1 and eGFR. eGFR, estimated glomerular filtration rate; NAG, N-acetyl-β-D-glucosaminidase; Trx-1, thioredoxin-1; UACR, urinary microalbumin–creatinine ratio; UBCR, urinary β_2-microglobulin concentration to creatinine ratio.

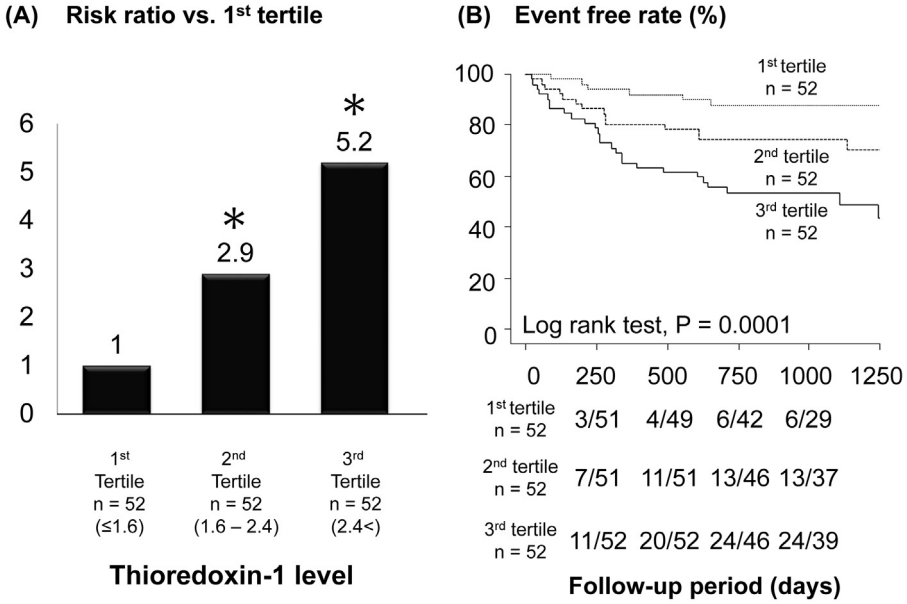

Fig. 4. (A) Cox proportional hazard regression analysis. Hazard ratio relative to the first tertile. *$p < 0.05$ vs. first tertile. (B) Kaplan–Meier analysis of all cardiac events in patients in the three groups based on thioredoxin-1 level.

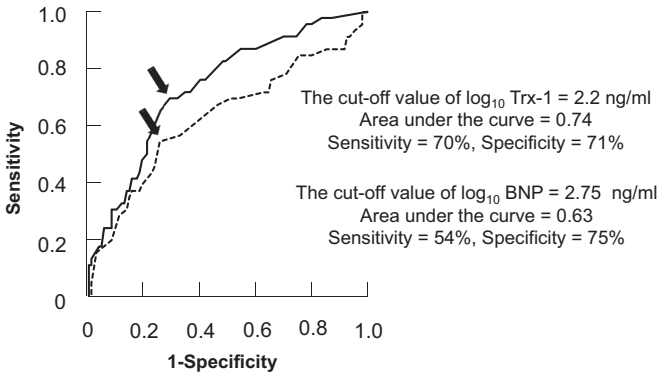

Fig. 5. The receiver operating characteristics curve of Trx-1 for future cardiac events. The area under the curve, sensitivity, and specificity of Trx-1 were 0.72, 68%, and 70%, respectively. Trx-1, thioredoxin-1; BNP, brain natriuretic peptide.

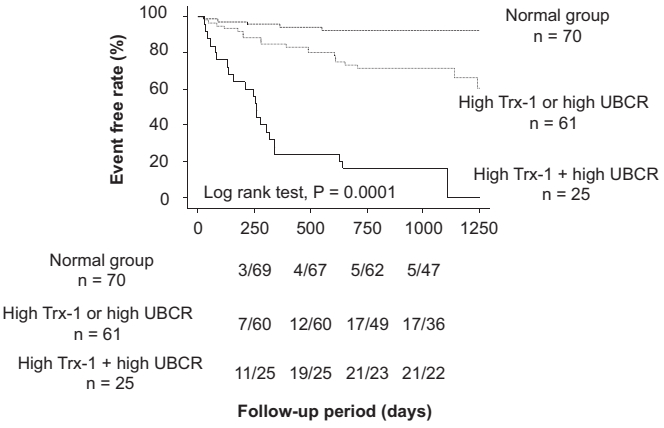

Fig. 6. Kaplan–Meier analysis of all cardiac events. High Trx-1 + high UBCR group had the greatest risk in patients with chronic heart failure. Trx-1, thioredoxin-1; UBCR, urinary β_2-microglobulin concentration to creatinine ratio.

identify plasma Trx-1 as a useful marker to identify patients at high risk for the related comorbidities of HF and renal tubular damage.

Limitations

First, we were unable to confirm the precise mechanism of Trx-1 secretion in this prospective observational study. Second, since this study performed one-time measurement of plasma Trx-1, serial changes in plasma Trx-1 in response to symptom improvement were not confirmed. Third, the study number was relatively small. A study using a greater number of patients is needed to determine the prognostic value of plasma Trx-1. Finally, in the present study, optimal medical therapy was independently administered based on symptom improvements, physical examination, and chest X-ray findings by the physicians who were blinded to the results of the biochemical analyses. Thus, β-blocker was properly administered to patients with severe CHF. This may contribute to the result that patients with cardiac events took more β-blocker than those without it.

Conclusion

Plasma Trx-1 level was associated with renal tubular damage and was predictive of cardiac prognosis. Plasma Trx-1 could be a useful marker to identify patients at increased risk for comorbid HF and renal tubular damage.

Conflict of interest

None declared.

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