SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2010; 27; 27-35

Significance of plasma NT-proBNP levels as a biomarker in the assessment of cardiac involvement and pulmonary hypertension in patients with sarcoidosis

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Abstract.*Background:* Cardiac involvement and pulmonary hypertension (PH) are life-threatening complications in sarcoidosis. *Objective:* This study aimed to investigate the utility of plasma NT-proBNP in the assessment of these conditions in sarcoidosis patients. *Study Design and Methods:* A prospective, observational study was performed on 150 consecutive Japanese sarcoidosis patients. Doppler echocardiography was performed in all subjects, and those who were successfully evaluated for PH status were included in the analysis. Cardiac sarcoidosis was diagnosed based on Japanese guidelines, and PH was defined as estimated systolic pulmonary artery pressure (sPAP) ≥ 35 mmHg. The diagnostic accuracy of NT-proBNP according to the presence of cardiac sarcoidosis and PH was assessed based on receiver-operator characteristic (ROC) curves. *Results:* 130 subjects were successfully evaluated for PH status. Of these, 29 met the diagnostic criteria of cardiac sarcoidosis, and 21 were diagnosed with PH. Plasma NT-proBNP levels were significantly higher in patients with cardiac sarcoidosis ($p<0.0001$). Stepwise regression analysis showed that presence of cardiac sarcoidosis, decreased ejection fraction and increased sPAP were all independently associated with higher plasma NT-proBNP levels. Plasma NT-proBNP showed good accuracy in identifying patients with cardiac sarcoidosis (area under the ROC curve; AURC = 0.913). However, even when patients with cardiac sarcoidosis were excluded, plasma NT-proBNP levels could not be used reliably to identify patients with PH (AURC = 0.681). *Conclusion:* In patients with sarcoidosis, plasma NT-proBNP levels are a useful biomarker to identify cardiac involvement, but not to identify PH. *(Sarcoidosis Vasc Diffuse Lung Dis 2010; 27: 27-35)*

Key words: heart failure, NT-proBNP, pulmonary hypertension, ROC curves

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology. Advanced lung disease is the leading cause of death of patients with sarcoidosis in most Western countries, while in Japan it is cardiac sarcoidosis (1). Previous studies have shown that pulmonary hypertension (PH) is quite common in sarcoidosis, especially in the advanced stages of lung

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disease (2, 3). In addition, it has been reported that PH was related to poor survival in sarcoidosis (4). Thus, the evaluation of cardiac involvement and PH is crucial in the management of sarcoidosis patients.

B-type natriuretic peptide (BNP) belongs to the family of natriuretic peptides. In response to wall stress, pre-proBNP in synthesized in the ventricular myocardium, and the peptide is cleaved first to $proBNP_{1-108}$, then to the biologically active BNP_{1-32} and the inactive amino-terminal fragment NT-proBNP (5, 6). Serum levels of BNP and NT-proBNP are increased in many clinical situations that cause overload of left or right ventricles, such as congestive heart failure, acute coronary syndromes, pulmonary embolism, atrial fibrillation, and pulmonary diseases with right heart failure (5, 7). In addition, Leuchte et al. reported that serum BNP correlated with pulmonary hemodynamics, and that it is a useful marker for the evaluation of PH in patients with lung fibrosis (8). Based on these reports, BNP and NT-proBNP may be potential biomarkers for the evaluation of cardiac involvement and PH in sarcoidosis. However, there have been only a few reports that have evaluated the utility of plasma BNP in the diagnosis of cardiac sarcoidosis (9, 10).

Although the measurement of both BNP and NT-proBNP plasma levels can be used in patient management (5), NT-proBNP levels are considered to give more consistent results than those of BNP, which may vary significantly depending on the assay used (11). Thus, NT-proBNP plasma levels were used in this study.

The aim of this study was to investigate the utility of measuring NT-proBNP plasma levels in the assessment of cardiac involvement and PH in sarcoidosis patients.

Materials and methods

Study population

The study population comprised 150 Japanese sarcoidosis patients with histological confirmation of the diagnosis. All patients were followed consecutively at the outpatient sarcoidosis clinic in the Central Clinic of Kyoto during the period between June and November 2008. Patients with concurrent collagen vascular diseases and other lung diseases were excluded from the study, as were those with cardiac diseases (ischemic heart disease, valvular disease, hypertrophic cardiomyopathy) that could not be attributed to sarcoidosis. The study was approved by the ethics committees in Kyoto Central Clinic/Clinical Research Center, and informed, written consent was obtained from all subjects.

Doppler echocardiography (DE) technique and measurement of systolic pulmonary artery pressure (sPAP)

Doppler echocardiography (DE) was performed on the same day as the NT-proBNP measurements. Conventional clinical echocardiographic equipment (ProSound SSD-6500SV, ALOKA. Co., Ltd, Tokyo, Japan) was used, and systolic pulmonary artery pressure (sPAP) and EF were measured according to a previously reported method (2). Briefly, right atrial pressure (RAP) was estimated by measuring the percent collapse of inferior vena cava diameter during inspiration, and transtricuspid gradient was estimated based on the modified Bernoulli equation. sPAP was calculated as the sum of RAP and transtricuspid gradient. PH was defined as an sPAP of more than 35 mmHg; this definition was based on previous reports (12, 13). PH was not evaluated in patients negative for transtricuspid regurgitant flow, and these patients were therefore excluded from the analyses.

Assessment of cardiac sarcoidosis

All patients were evaluated for cardiac sarcoidosis based on the diagnostic criteria of Japanese Ministry of Health and Welfare; this study used the 2006 revised version of the original 1993 diagnostic guidelines (14). Firstly, all patients were assessed to see if they fulfilled the major diagnostic criteria based on echocardiography (ECG), DE and gallium-67 citrate-scintigraphy findings. Secondly, patients who fulfilled only one of these major criteria were further assessed for minor criteria based on Holter ECG, thallium-201 chloride scintigraphy and/or cardiac magnetic resonance imaging (MRI).

Measurement of plasma NT-proBNP levels

Plasma NT-proBNP levels was measured on the same day as the DE procedure by the ECLusys

2010® analyzer (Roche Diagnostics) using an electrochemiluminescent assay (15).

Measurement of serum angiotensin converting enzyme (sACE)

Serum angiotensin converting enzyme (sACE) activity was measured by Kasahara's method (16) using optical density measurements at 505 nm and 800 nm with a spectrophotometer. Serum samples were considered to be positive if they contained more than 21.4 IU/L.

Pulmonary function tests (PFTs)

All PFTs were performed according to the American Thoracic Society guidelines (17, 18). Vital capacity (VC), forced vital capacity (FVC), and the diffusion capacity of carbon monoxide (DLCO) were measured using Chestac-8800 (Chest M.I., Inc., Tokyo, Japan). Published equations for adults were used to determine predicted values of each parameter (19, 20).

Assessment of other clinical parameters

Classification of chest radiographs (Stage 0: normal; Stage I: bilateral hilar lymphadenopathy (BHL); Stage II: BHL with pulmonary infiltrations; Stage III: pulmonary infiltrates without BHL; Stage IV: pulmonary fibrosis) was performed and the number of extrapulmonary lesions (1) were recorded.

Statistical analysis

Comparison of categorical data was made using the χ^2 test, or the Fisher exact probability test. Continuous variables were compared with Man-Whitney U test. We applied linear, logarithmic, power and exponential regression models to estimate the relationship between plasma NT-proBNP levels and EF, and sPAP. The exponential model provided the best fit for the data. Thus, we used the log-transformed NT-proBNP levels (log NT-proBNP) to show the relationships between these indices. Spearman rank correlation coefficient was used to analyze the correlation between two samples. Stepwise regression analyses were performed to investigate the independent effect of cardiac sarcoidosis, EF, sPAP, age, gender, body mass index (BMI) and serum creatinine on log NT-proBNP. Receiver Operating Characteristic (ROC) curves were used to define the appropriate cut-off values of NT-proBNP in relation to cardiac sarcoidosis and PH, and the sensitivity and specificity were determined. The area under the ROC curves (AURC) was calculated and a value above 0.80 was considered as good discrimination (21). The statistics were generated using JMP for Windows, version 6 (SAS Institute, Inc., Cary, NC, USA). All tests were two-tailed and the level of significance was set at 0.05.

Results

Frequency of cardiac sarcoidosis and PH

Of the 150 consecutive patients comprising the study population, PH status was successfully evaluated in 130 (87%), and these therefore formed the population for further analysis. Patient demographics and laboratory data for the 130 patients, together with the frequencies of cardiac sarcoidosis and PH, are shown in Table 1; 29 patients (22%) met the

Table 1. Demographics and clinical data of the study population

Number of patients	130
Age, yrs	61 (30-82)
Sex, M/F	36/94
Body Mass Index, kg/m^2	22.6 (16.8-34.5)
Disease duration, months	84 (1-377)
Stage, 0/I/II/III/IV	32/51/32/12/3
Number of extrathoracic lesions*	1 (0-5)
NT-pro BNP, pg/ml	77.5 (6-4226)
sACE, IU/L	15.3 (2.5-55.8)
Serum creatinine, mg/dl	0.69 (0.48-1.15)
Systemic treatment, N (%)‡	58 (45%)
Vasodilator, N (%)¶	29 (22%)
%VC, %	104.0 (60.6-142.6)
%DLCO, %	87.3 (34.8-176.3)
Cardiac sarcoidosis, N (%)	29 (22%)
Pulmonary hypertension, N (%)	20 (15%)
Ejection fraction, %	68.8 (23.2-83.0)
sPAP, mmHg	29.6 (12.9-69.0)

Data are expressed as median (range) or number (percentage).
* Number of cases: eye 90, skin 35, heart 29, spleen 10, superficial lymph nodes 10, kidney 9, nerve 7, liver 7, muscle 4, hypercalcemia 2, and bone 1.
‡ Previous or current treatment with oral corticosteroids, immunosuppressants, or minocyclines.
¶ Current treatment with calcium channel blockers, angiotensin II receptor antagonists, prostacyclines, phosphodiesterase inhibitors or endothelin receptor antagonists.

Table 2. Comparison of clinical data between patients with and without cardiac sarcoidosis

	Cardiac sarcoidosis		p-value
	+	-	
Number of patients	29	101	
Age, yrs	62 (31-82)	61 (30-81)	NS
Sex, M/F	7/22	29/72	NS
Body Mass Index, kg/m^2	23.6 (17.5-30.2)	22.6 (16.8-34.5)	NS
Disease duration, months	70 (4-196)	86 (1-377)	NS
Stage, 0/I/II/III/IVÅ	10/11/5/3/0	22/40/27/9/3	NS
Number of extrathoracic lesions	2 (1-5)	1 (0-5)	<0.0001
NT-pro BNP, pg/ml	424.0 (46.0-4226.0)	64.0 (6.0-680.0)	<0.0001
sACE, IU/L	13.2 (2.5-29.3)	16.8 (6.3-55.8)	<0.001
Serum creatinine, mg/dl	0.76 (0.51-1.15)	0.67 (0.48-1.14)	<0.01
Systemic treatment*	26 (90%)	32 (32%)	<0.0001
Vasodilator‡	16 (55%)	13 (13%)	<0.0001
%VC, %	98.3 (68.5-130.7)	105.4 (60.6-142.6)	NS
%DLCO, %	77.8 (45.1-97.3)	88.2 (34.8-176.3)	<0.01
Pulmonary hypertension	5 (17%)	15 (15%)	NS
Ejection fraction, %	52.2 (23.2-79.6)	71.1 (51.0-83.0)	<0.0001
sPAP, mmHg	30.1 (12.9-69.0)	29.3 (13.8-47.3)	NS

Data are expressed as median (range) or number (percentage).
* Previous or current treatment with oral corticosteroids, immunosuppressants, or minocyclines.
‡ Current treatment with calcium channel blockers, angiotensin II receptor antagonists, prostacyclines, phosphodiesterase inhibitors or endothelin receptor antagonists.

diagnostic criteria of cardiac sarcoidosis, and 20 (15%) were diagnosed with PH.

Comparison of plasma NT-proBNP levels and clinical parameters between patients with and without cardiac sarcoidosis

As shown in Table 2, plasma NT-proBNP levels were significantly higher in patients with cardiac sarcoidosis (median 424.0, range 46.0-4226.0 pg/ml), compared with those without (median 64.0, range 6.0-680.0 pg/ml) ($p<0.0001$, Fig 1A). In addition, on average, patients with cardiac sarcoidosis had a greater number of extrathoracic lesions, lower sACE levels, higher serum creatinine levels, lower %DLCO, and a lower EF. They were more frequently treated with vasodilators and systemic steroids or immunosuppressants compared with those without cardiac sarcoidosis.

Comparison of plasma NT-proBNP levels and clinical parameters between patients with and without PH

As shown in Table 3, patients with PH had significantly higher levels of plasma NT-proBNP (median 140.0, range 26.0-2758.0 pg/ml) compared with those without (median 73.5, range 6.0-4226.0 pg/ml) ($p<0.05$, Table 3, Fig 1B). However, the increase of NT-proBNP in patients with PH was milder than in patients with cardiac sarcoidosis (Fig 1A). Although most clinical parameters were unchanged in patients with PH, they had decreased %VC compared to those without the condition.

Correlations between EF and plasma NT-proBNP levels

There was a significant negative correlation between EF measured by DE and plasma NT-proBNP levels when the analysis was conducted in all patients, regardless of the presence of cardiac sarcoidosis, and this association was exponential ($r = -0.188$, $p<0.05$, Fig 2A). The correlation was even stronger when the analysis was restricted to patients with cardiac sarcoidosis ($r = -0.663$, $p<0.001$, Fig 2B).

Correlations between sPAP and plasma NT-proBNP levels

Although there was no correlation between sPAP and plasma NT-proBNP levels in patients with cardiac sarcoidosis (data not shown), there was a significant positive correlation between these parameters in the overall patient population (Fig 3A, $r = 0.347$, $p<0.0001$), and in patients without cardiac sarcoidosis (Fig 3B, $r = 0.347$, $p<0.001$).

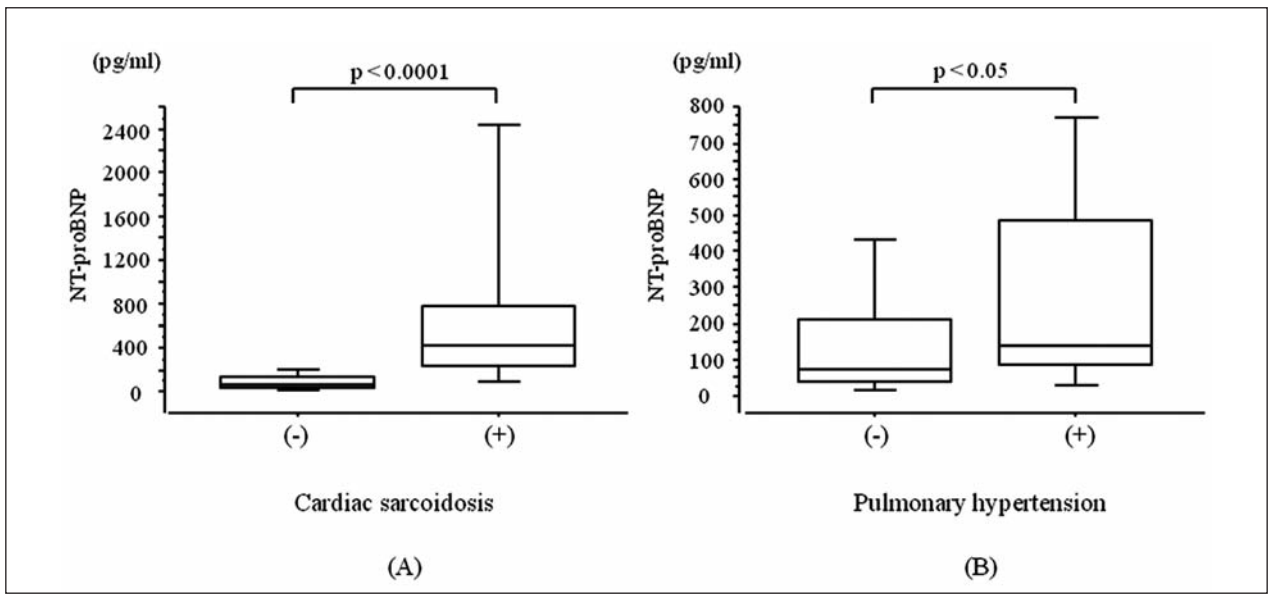

Fig. 1. Comparison of plasma NT-proBNP levels among subgroups. (A). Comparison between patients with and without cardiac sarcoidosis. Plasma NT-proBNP levels were significantly higher in patients with cardiac sarcoidosis (p<0.0001). (B). Comparison between patients with and without pulmonary hypertension. Plasma NT-proBNP levels were higher in patients with pulmonary hypertension, although the difference was relatively weak (p<0.05). Mann-Whitney U test was used in the statistical analysis

Table 3. Comparison of clinical data between patients with and without pulmonary hypertension

	Pulmonary hypertension		p-value
	+	-	
Number of patients	20	110	NS
Age, yrs	68 (34-78)	61 (30-82)	NS
Sex, M/F	7/13	29/81	NS
Body Mass Index, kg/m^2	22.3 (17.5-30.2)	22.7 (16.8-34.5)	NS
Disease duration, months	64 (8-371)	84 (1-377)	NS
Stage, 0/I/II/III/IV	3/8/5/4/0	29/43/27/8/3	NS
Number of extrathoracic lesions	1 (0-5)	1 (0-5)	NS
NT-pro BNP	140.0 (26.0-2758.0)	73.5 (6.0-4226.0)	<0.05
sACE, IU/L	14.3 (3.8-55.8)	15.3 (2.5-37.6)	NS
Serum creatinine, mg/dl	0.71 (0.48-1.14)	0.68 (0.48-1.15)	NS
Systemic treatment*	10 (50%)	48 (44%)	NS
Vasodilator‡	6 (30%)	23 (21%)	NS
%VC, %	98.1 (60.6-132.9)	104.8 (61.3-142.6)	<0.05
%DLCO, %	86.8 (40.3-109.0)	87.5 (34.8-176.3)	NS
Cardiac sarcoidosis	5 (25%)	24 (22%)	NS
Ejection fraction, %	72.7 (37.4-79.6)	68.4 (23.2-83.2)	NS
sPAP, mmHg	38.3 (35.3-69.0)	28.6 (12.9-35.0)	<0.0001

Data are expressed as median (range) or number (percentage).
* Previous or current treatment with oral corticosteroids, immunosuppressants, or minocyclines.
‡ Current treatment with calcium channel blockers, angiotensin II receptor antagonists, prostacyclines, phosphodiesterase inhibitors or endothelin receptor antagonists.

Independent factors associated with plasma levels of NT-proBNP

To investigate independent determinants of plasma NT-proBNP levels, stepwise regression analysis was performed. Presence of cardiac involvement, EF, sPAP, patient age, gender, serum creatinine and BMI were included in the analysis as independent variables. In this study, there were exponential correlations between EF, sPAP and NT-proBNP.

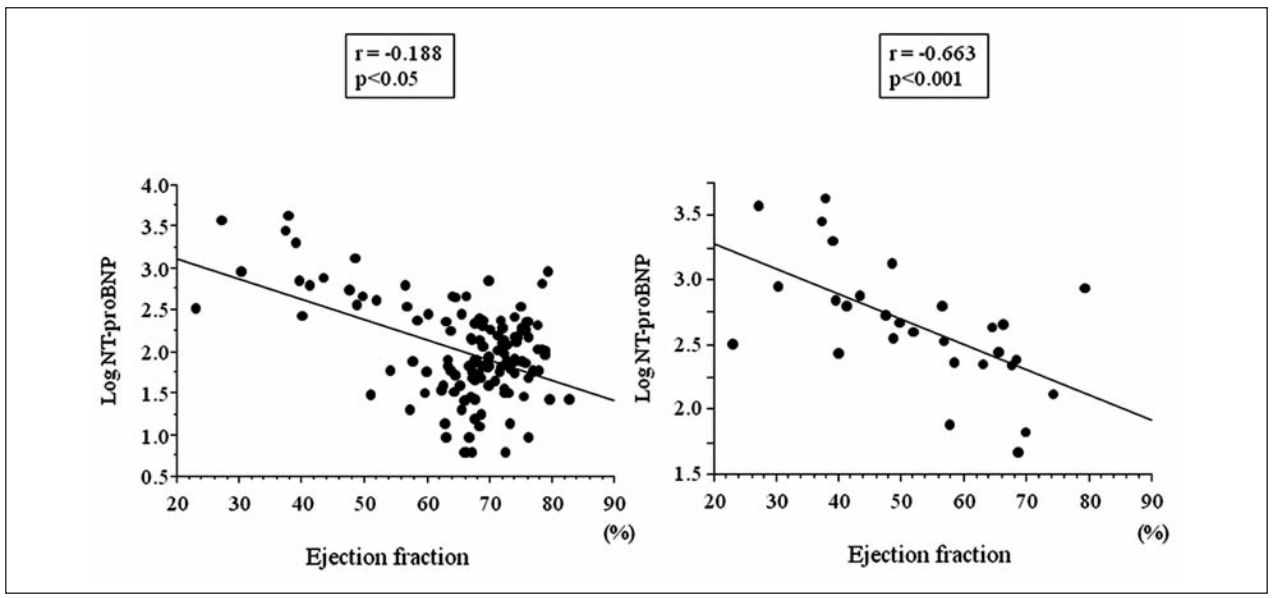

Fig. 2. Correlation between cardiac ejection fraction measured by Doppler echocardiography and plasma NT-proBNP levels. Plasma NT-proBNP levels are shown in the logarithmic scale (in pg/ml). (A) Total patients (n=130). There was a significant negative correlation between ejection fraction and NT-proBNP (r = -0.188, p<0.05). (B) Patients with cardiac sarcoidosis (n=29). The correlation between the parameters was stronger (r = -0.663, p<0.001) than that among "total" study patients. Analysis was performed with the Spearman rank correlation coefficient

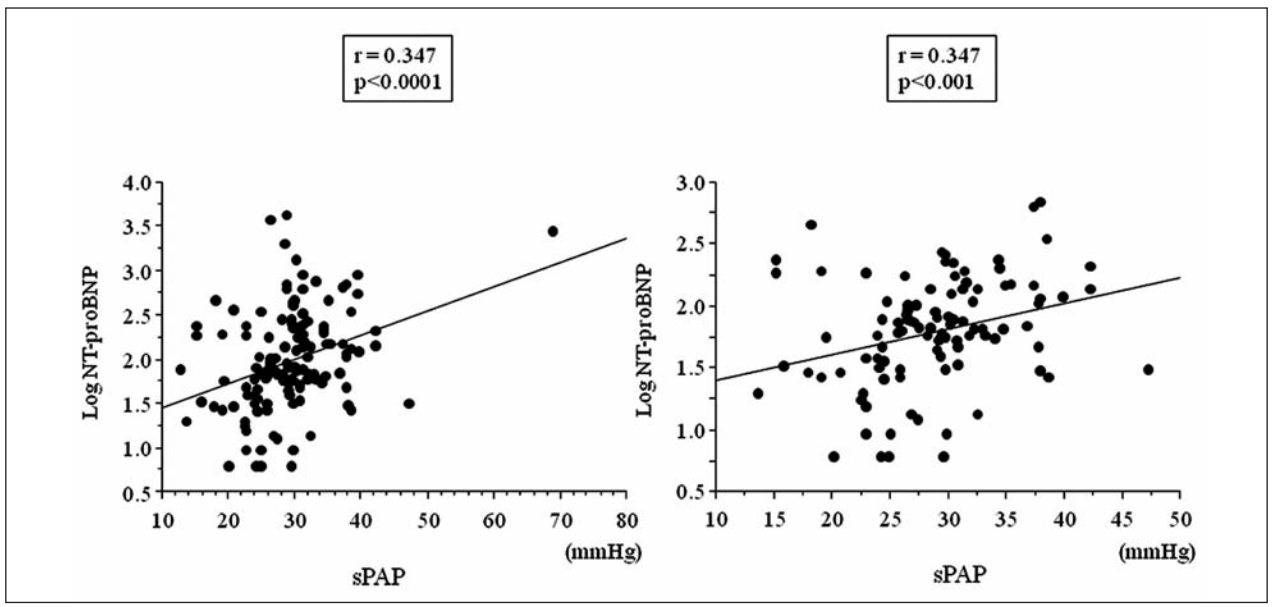

Fig. 3. Correlation between systolic pulmonary artery pressures (sPAP) estimated by Doppler echocardiography and plasma NT-pro BNP levels. Plasma NT-proBNP levels are shown in the logarithmic scale (in pg/ml). (A) Total patients (n=130). There was a significant positive correlation between sPAP and NT-proBNP (r = 0.347, p < 0.0001). (B) Patients without cardiac sarcoidosis (n = 101). Similarly, there was a significant positive correlation between sPAP and NT-proBNP (r = 0.347, p < 0.001). Analysis was performed with the Spearman rank correlation coefficient.

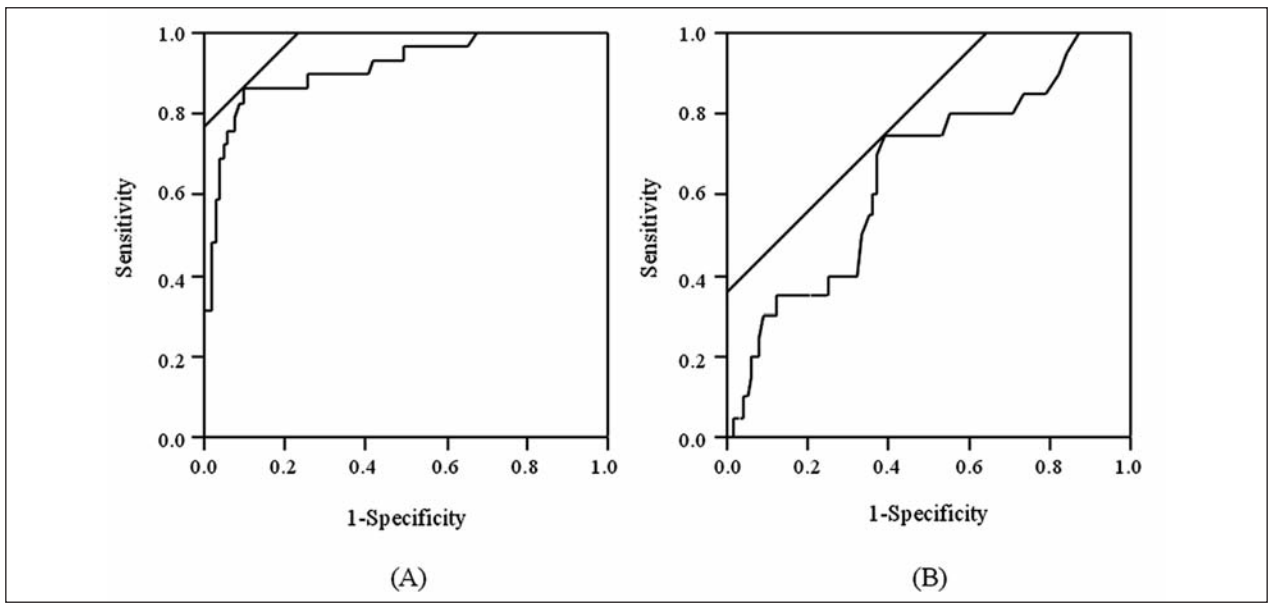

Fig. 4. (A) Discriminative power of plasma NT-proBNP levels to cardiac sarcoidosis. AURC = 0.913; cut-off: 213 pg/ml; sensitivity: 86.2%; specificity: 90.1%. (B) Discriminative power of plasma NT-proBNP levels to pulmonary hypertension. AURC = 0.650; cut-off: 103 pg/ml; sensitivity: 75.0%; specificity: 60.9%. AURC: Area under ROC curve

In addition, a previous study also showed an exponential association between degree of renal failure and NT-proBNP (22), thus log NT-proBNP was used as the dependent variable. The analysis showed that cardiac involvement (regression coefficient: 0.569), decreased EF (regression coefficient: -0.011), increased sPAP (regression coefficient: 0.013), older age (regression coefficient: 0.012), female gender (regression coefficient: 0.254), increased serum creatinine (regression coefficient: 0.004) and decreased BMI (regression coefficient: -0.032) were all independently associated with higher log NT-proBNP ($p<0.0001$, R-square: 0.645).

Discriminative power of plasma levels of NT-proBNP

Discriminative power of plasma levels of NT-proBNP with regard to cardiac sarcoidosis and PH were assessed based on ROC curves. The result showed that plasma NT-proBNP levels had good discriminative capacity for cardiac sarcoidosis with an AURC of 0.913 (Fig 4A). The best cut-off value was 213 pg/ml for NT-proBNP, with a sensitivity of 86.2%, and a specificity of 90.1% to discriminate cardiac sarcoidosis. On the other hand, NT-proBNP had a poor discriminative capacity for PH, with an AURC of 0.650 (Fig 4B). For the discrimination of PH, the optimal cut-off value was 103 pg/ml, and the sensitivity and the specificity were 75.0% and 60.9%, respectively. Even when patients with cardiac sarcoidosis were excluded, plasma NT-proBNP levels could not reliably identify the presence of PH (AURC = 0.681).

Discussion

In this study, we showed that plasma NT-proBNP levels were markedly elevated in patients with cardiac sarcoidosis, and that they were affected by cardiac involvement, EF, sPAP, patient age, gender, serum creatinine and BMI. It was also confirmed that plasma NT-proBNP is a useful biomarker for indicating a possible cardiac involvement in sarcoidosis.

It has been recognized that performance characteristics of BNP and NT-proBNP are similar, and their levels are correlated, thus either can be used in patient management (5). In previous large cohort studies, it has been shown that the measurement of

plasma BNP (23) and NT-proBNP (24) levels were useful in emergency departments in the diagnosis of heart failure as a cause of dyspnea. Although conflicting data exist, some studies have shown the superiority of NT-proBNP over BNP in the detection of left ventricular dysfunction (11, 25). In the present study, NT-proBNP was used because BNP results may vary significantly depending on the assay used, whereas NT-proBNP are more likely to give consistent results (11).

It has been reported that plasma NT-proBNP levels are also elevated in advanced age (25, 26), female gender (22, 26), and renal dysfunction (22, 27), and that they may also be influenced by obesity (28). Thus, these factors were included in the regression analysis to investigate independent factors that affect plasma NT-proBNP levels. According to the result of this study, not only the decreased EF, but also the presence of cardiac sarcoidosis itself was independently associated with increased plasma NT-proBNP. Yasutake et al. evaluated plasma ANP and BNP levels in 37 and 44 sarcoidosis patients, respectively, and found that they had poor diagnostic accuracy for cardiac sarcoidosis, although they could successfully discriminate those with cardiac complications, such as high degree atrioventricular block, congestive heart failure and tachyarrhythmias (9). On the other hand, Date et al. reported that plasma BNP levels were elevated in patients with cardiac sarcoidosis even when their ejection fraction (EF) was preserved**;** however**,** their study population included those with pacemaker implantations and ventricular arrhythmias (10). In our study population, only three patients had cardiac sarcoidosis without any cardiac complications; however, two of these patients had elevated plasma NT-proBNP levels (273 and 861 pg/ml), suggesting that plasma NT-proBNP levels are elevated in some patients with cardiac sarcoidosis who do not have any cardiac complications. Further investigation is necessary to elucidate whether plasma NT-proBNP levels are elevated in sarcoidosis patients with this clinical situation.

sPAP was also found to be an independent factor associated with plasma NT-proBNP levels, and there was a significant positive correlation between sPAP and plasma NT-proBNP levels in the overall patient group (Fig 3A) and in patients without cardiac sarcoidosis (Fig 3B). However, the diagnostic accuracy of plasma NT-proBNP for PH was poor, even when patients with cardiac sarcoidosis were excluded. The severity of PH was relatively mild in our study population due to the majority of subjects having mild lung disease with preserved lung functions (Table 1). Further investigations using patients with more severe PH might show different results regarding the diagnostic accuracy of plasma NT-proBNP for PH and cardiac involvement.

Although cardiac involvement is sometimes life-threatening to sarcoidosis patients, its diagnosis is challenging. Due to the inhomogeneous distribution of cardiac involvement, the diagnostic rate of endomyocardial biopsy is as low as less than 20% (29). Thus, the diagnosis of cardiac sarcoidosis is now based on the combination of several physiological tests and nuclear medicine (1, 14). Based on the result of this study, plasma NT-proBNP levels may be a candidate biomarker for inclusion in the diagnostic criteria of cardiac sarcoidosis. Among the patients whose plasma NT-proBNP exceeded 213 pg/ml, seven did not fulfill the criteria of cardiac sarcoidosis or PH. Among these patients, one had first degree atrio-ventricular block, and another had premature ventricular contraction of Lown Grade 2. These patients might have had subclinical cardiac sarcoidosis.

In this study, older age, female gender, increased serum creatinine and decreased BMI were all independently associated with higher log NT-proBNP plasma levels. This is compatible with the results of previous studies which investigated patients in other clinical settings (22, 25-28). In sarcoidosis patients, these factors should also be taken into account when interpreting plasma NT-proBNP levels.

The limitation of this study is that right heart catheterization (RHC) was not performed to evaluate PH. It has been reported that sPAP estimated by DE does not serve as an accurate predictive model of sPAP measured by RHC (30, 31); thus, the data on PH in this study should be interpreted with caution. Despite the limitation, this is the first large cohort to show the usefulness of measuring plasma NT-proBNP levels in the assessment of cardiac sarcoidosis.

In conclusion, decreased ventricular function and increased pulmonary artery pressure are both associated with higher NT-proBNP levels in patients with sarcoidosis. Plasma NT-proBNP levels are a useful biomarker for indicating possible cardiac involvement in sarcoidosis.

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