【 ORIGINAL ARTICLE 】

Associations of the Prognostic Nutritional Index with the Cardiac Function and Survival after Cardiac Resynchronization Therapy

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Abstract:

Objective   The relationship between changes in the nutritional status after cardiac resynchronization therapy (CRT) and the prognosis has not been fully elucidated. We aimed to evaluate the changes in the nutritional status as assessed by the prognostic nutritional index (PNI) and their associations with the improvement in the cardiac function and subsequent clinical outcomes.

Methods   The study population consisted of 119 patients with a CRT-device. They were divided into 2 groups, based on whether their PNI had increased at 6 months after CRT-device implantation (positive ΔPNI group, n=73) or not (negative ΔPNI group, n=46). The left ventricular (LV) end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV ejection fraction (LVEF) were measured before and six months after CRT-device implantation. We compared the changes in the cardiac function and prevalence of adverse events (re-hospitalization due to worsening heart failure or all cause death) between the two groups.

Results   In the positive ΔPNI group, the LVEDV (186±93 mL vs. 149±71 mL, p<0.05) and LVESV (134± 75 mL vs. 98±62 mL, p<0.05) were significantly decreased 6 months after CRT-device implantation. In addition, the LVEF (31±11% vs. 37±12%, p<0.05) was significantly increased after CRT-device implantation. In the negative ΔPNI group, no significant changes were observed in any echocardiographic parameters. During a median follow-up period of 914 days, there were 67 (56.3%) adverse events. In the Kaplan-Meier analysis, the positive ΔPNI group was associated with a lower risk of adverse events than the negative ΔPNI group (50.6% vs. 65.2%, log-rank p=0.042).

Conclusion   Our results suggest that improvement in the cardiac function after CRT-device implantation is associated with increases in the PNI, resulting in favorable outcomes.

Key words: adverse event, cardiac function, cardiac resynchronization therapy, nutritional status, prognostic nutritional index

Introduction

Cardiac resynchronization therapy (CRT) is a well-established therapy for patients who have symptomatic heart failure (HF) despite undergoing optimal medical treatment. Several studies have shown that CRT improves the quality of life and cardiac function as well as the survival in patients with HF (1-3). However, there is wide variability in the extent of ventricular remodeling and improvement in the clinical status in HF patients with a CRT-device, and some patients have not responded to CRT, resulting in poor clinical outcomes (1, 4).

Malnutrition is often seen in patients with HF due to a low nutritional intake, absorption disorder, decreased immune system function, and increased resting metabolic

rate (5, 6). Consequently, progression of malnutrition is associated with the exacerbation of fluid retention, inflammation, and neurohormonal activation, which lead to a poor prognosis in patients with HF (7, 8). Several nutritional screening tools have been proposed for assessing malnutrition and subsequent long-term mortality in patients with HF. Among them, the prognostic nutritional index (PNI) is calculated from the serum albumin concentration and total lymphocyte count as a simple predictor of long-term mortality in patients with HF (9, 10). Therefore, changes in the PNI after CRT-device implantation may be associated with improvement in the cardiac function and subsequent clinical outcomes; however, these associations have not yet been fully elucidated.

The present study therefore evaluated changes in the nutritional status, assessed by the PNI, and their associations with improvement in the cardiac function and subsequent prognosis in patients with a CRT-device.

Materials and Methods

Study subjects

This was a retrospective study of 126 HF patients who had undergone successful CRT-device implantation between 2008 and 2018 at our institution.

Before CRT-device implantation, blood sampling, 12-lead electrocardiography and echocardiography were performed to evaluate the clinical status. The eligibility criteria for CRT were New York Heart Association (NYHA) class II-IV symptoms of HF despite receiving optimal medical therapy, a left ventricular (LV) ejection fraction (LVEF) of ≤35% on echocardiography, and left bundle branch block with a QRS duration of ≥120 ms, in accordance with established criteria (11, 12). An extensive evaluation, including the assessment of blood samples as well as echocardiography, was performed for all patients six months after CRT-device implantation. Patients who died within the 6-month follow-up period were excluded from this study (n=7).

Next, the patients (n=119) were divided into 2 groups based on whether their PNI had increased at 6 months after CRT-device implantation (positive ΔPNI group, n=73) or not (negative ΔPNI group, n=46). We assessed the effect of changes in the PNI after CRT-device implantation on the laboratory data, cardiac function, and outcomes.

Written informed consent was obtained from all study subjects. The study protocol was approved by the ethics committee of Fukushima Medical University.

Device implantation

Device implantation was performed when the HF was relatively compensated. A coronary sinus venogram was performed using a balloon catheter. The LV lead was inserted transvenously via the subclavian route. Next, the LV pacing lead was inserted through the coronary sinus and positioned in the venous system, preferably in a posterolateral vein and

a non-apical site. The right atrial and ventricular leads were conventionally positioned in the right atrial appendage and the apex of the right ventricle, respectively. Finally, all leads were connected to a biventricular cardiac device.

Data collection

The laboratory findings and outcomes of 119 patients who received CRT implantation with a defibrillator (CRT-D, n=113) or with a pacemaker (n=6) were analyzed before and 6 months after CRT-device implantation. Laboratory data included hemoglobin, total lymphocyte count, albumin, total bilirubin, blood urea nitrogen (BUN), creatinine, the estimated glomerular filtration rate (eGFR), sodium, c-reactive protein (CRP), brain natriuretic peptide (BNP), and the PNI. The PNI was calculated as follows: PNI=10×serum albumin (g/dL)+0.005×total lymphocytes (count per mm^3) (9). The eGFR was determined based on the Modification of Diet in Renal Disease formula (13). The echocardiographic parameters included the LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LVEF, and tricuspid regurgitation pressure gradient (TRPG).

Changes in all parameters (Δ) were determined as the difference in values before and six months after CRT-device implantation. In the present study, a response to CRT was defined as a reduction of ≥15% in the LVESV by 6 months after CRT-device implantation (14, 15).

Identification of adverse events during the follow-up

The follow-up of adverse events continued until March 2019. The adverse events were defined as re-hospitalization due to worsening HF or all-cause death. For patients that experienced two or more events, only the first event was included in the analysis. The diagnosis of worsening HF was determined using HF guidelines (16). The status and/or dates of death of all patients were obtained from the patients' medical records or attending physicians at the patient's referring hospital. All patients were followed in this study. The survival time was calculated from the date of CRT-device implantation until the date of re-hospitalization, death, or last follow-up.

Statistical analyses

Parametric variables were presented as the mean±standard deviation, and categorical variables were expressed as numbers and percentages. Parametric variables were compared using Student's t-test, and the chi-square test was used for comparisons of categorical variables. The paired Student's t-test was used to compare the changes in clinical parameters between pre-CRT-device implantation and six months after CRT-device implantation in each group. The cumulative incidence curve of adverse events was plotted via the Kaplan-Meier method, with statistical significance examined by the log-rank test. A value of $p<0.05$ was considered statistically significant. Statistical analyses were performed with the SPSS statistical software program (version 26.0, SPSS Insti-

Table 1.   Comparison of Baseline Clinical Characteristics for the Positive and Negative ΔPNI Groups.

	Positive ΔPNI group (n=73)	Negative ΔPNI group (n=46)	p value
Age	63.0±12.6	67.5±10.9	0.054
Male (n, %)	53 (72.6%)	33 (71.7%)	0.918
Body mass index, kg/cm^2	22.4±3.6	22.2±3.5	0.862
NYHA class III/IV (n,%)	30 (41.0%)	18 (39.1%)	0.831
Ischemic etiology (n, %)	13 (17.8%)	12 (26.0%)	0.953
Hypertension (n, %)	44 (60.2%)	28 (60.8%)	0.948
Diabetes (n, %)	37 (50.6%)	26 (56.5%)	0.534
Dyslipidemia (n, %)	56 (76.7%)	36 (78.2%)	0.844
Atrial fibrillation (n, %)	18 (24.6%)	14 (30.4%)	0.489
QRS>150 ms (n, %)	48 (65.7%)	30 (65.2%)	0.952
Medication			
β blockers (n,%)	73 (100.0%)	46 (100.0%)	1.000
ACE-inhibitors/ARBs (n,%)	66 (90.4%)	38 (82.6%)	0.212
Amiodarone (n,%)	38 (52.0%)	25 (54.3%)	0.807
Digitalis (n,%)	16 (21.9%)	9 (19.5%)	0.759

PNI: prognostic nutritional index, NYHA: New York Heart Association, ACE-inhibitors: angiotensin-converting enzyme-inhibitors, ARBs: angiotensin II receptor blockers

tute, Chicago, USA).

Results

Baseline characteristics

The baseline clinical characteristics of the present study's subjects are summarized in Table 1. The study subjects were divided into the positive ΔPNI (n=73) and negative ΔPNI (n=46) groups based on the ΔPNI at 6 months after CRT-device implantation, as described in the Methods. At baseline, there were no significant differences between the two groups in the age, gender, body mass index, medications, and prevalence of NYHA class III/IV, ischemic etiology, hypertension, diabetes, dyslipidemia, atrial fibrillation, or QRS duration >150 ms.

Laboratory and echocardiographic data

Regarding the laboratory data (Table 2), the albumin levels and PNI at baseline were significantly lower, whereas the eGFR and CRP levels at baseline were significantly higher, in the positive ΔPNI group than in the negative ΔPNI group. In the positive ΔPNI group, there was significant improvement in several parameters at 6 months after CRT-device implantation, including the hemoglobin, total lymphocyte count, albumin, total bilirubin, sodium, and BNP (p<0.05, respectively). In contrast, in the negative ΔPNI group, there was significant deterioration in several parameters at 6 months after CRT-device implantation, including hemoglobin, total lymphocyte count, albumin and creatinine (p<0.05, respectively). When changes in parameters at six months after CRT-device implantation were reanalyzed to compare between the positive and negative ΔPNI groups, a greater in-

crease in the Δhemoglobin, Δtotal lymphocyte count and Δalbumin and greater decrease in the ΔCRP were seen in the positive ΔPNI group than in the negative ΔPNI group.

Regarding the echocardiographic data (Table 3), at baseline, there were no significant differences between the two groups in the LVEDD, LVESD, LVEDV, LVESV, LVEF, or TRPG. In the positive ΔPNI group, there was significant improvement in several parameters at 6 months after CRT-device implantation, including the LVEDD, LVESD, LVEDV, LVESV, LVEF, and TRPG (p<0.05, respectively). However, in the negative ΔPNI group, no significant changes were found in any parameters. When changes in parameters at 6 months after CRT-device implantation were reanalyzed to compare between the positive and negative ΔPNI groups, a greater decrease in the ΔLVEDV and ΔLVSEV was seen in the positive ΔPNI group than in the negative ΔPNI group.

Changes in the PNI after CRT-device implantation and adverse events

During a median follow-up period of 914 days, there were 67 (56.3%) adverse events, including re-hospitalization due to HF (n=53) and death due to sudden death (n=6), HF (n=3), multiple organ failure (n=3), or malignancy (n=2). The incidence of adverse events was 50.6% and 65.2% in the positive and negative ΔPNI groups, respectively. In the Kaplan-Meier analysis, the positive ΔPNI group showed a lower risk of adverse events than the negative ΔPNI group during the follow-up period (log-rank p=0.042), as shown in Fig. 1.

Table 2.   Laboratory Data before and 6 Months after CRT-device Implantation.

Laboratory data		Positive ΔPNI group (n=73)	Negative ΔPNI group (n=46)	p value
Hemoglobin (g/dL)	Baseline	12.6±2.1	12.8±1.5	0.604
	6 months	13.2±1.8*	11.7±2.0*	
	Δ	0.5±1.6	-1.1±1.8	0.001
Total lymphocyte count (/mm³)	Baseline	1,296.5±494.0	1,427.4±482.8	0.159
	6 months	1,529.7±715.7*	1,156.5±405.6*	
	Δ	233.2±643.9	-270.9±403.1	<0.001
Albumin (g/dL)	Baseline	3.6±0.5	4.0±0.5	<0.001
	6 months	4.2±0.4*	3.7±0.6*	
	Δ	0.6±0.5	-0.3±0.3	<0.001
Total bilirubin (mg/dL)	Baseline	1.0±0.8	1.0±0.5	0.824
	6 months	0.9±0.5*	1.1±1.0	
	Δ	-0.2±0.4	0.1±0.9	0.075
Blood urea nitrogen (mg/dL)	Baseline	21.5±11.0	24.8±11.1	0.133
	6 months	21.5±9.8	24.5±11.0	
	Δ	-0.3±11.9	-0.3±8.7	0.999
Creatinine (mg/dL)	Baseline	1.06±0.39	1.23±0.50	0.053
	6 months	1.08±0.39	1.36±0.64*	
	Δ	0.02±0.25	0.12±0.38	0.096
eGFR (mL/min/1.73 m²)	Baseline	58.3±19.9	50.2±20.8	0.039
	6 months	55.8±18.6	47.4±21.6	
	Δ	-2.5±12.8	-2.7±12.0	0.912
Sodium (mEq/L)	Baseline	138.6±4.0	137.0±4.8	0.067
	6 months	140.0±2.6*	137.8±4.8	
	Δ	1.3±4.6	0.7±4.3	0.485
CRP (mg/dL)	Baseline	0.55±0.84	0.22±0.28	0.003
	6 months	0.30±0.73	0.52±1.20	
	Δ	-0.25±1.14	0.29±1.23	0.017
BNP (pg/mL)	Baseline	422.6±347.9	450.2±658.7	0.770
	6 months	278.8±431.3*	431.1±479.5	
	Δ	-143.8±481.6	-19.0±618.9	0.229
PNI	Baseline	42.4±6.1	46.7±6.3	<0.001
	6 months	49.5±5.7*	42.6±7.3*	
	Δ	7.0±5.8	-4.0±4.1	<0.001

*p<0.05 vs. Baseline.

CRT: cardiac resynchronization therapy, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, BNP: brain natriuretic peptide, PNI: prognostic nutritional index

Functional response to CRT and changes in the PNI after CRT-device implantation

In the present study, a functional response to CRT, defined as a reduction ≥15% in LVESV, was observed in 68 (57.1%) patients. The prevalence of CRT responders was significantly higher in the positive ΔPNI group than in the negative ΔPNI group (65.7% vs. 43.4%, p=0.017), as shown in Fig. 2.

In the subgroup analysis, changes in the PNI after CRT-device implantation were compared between the CRT responders (n=68) and the non-responders (n=51). At baseline, there was no significant difference in the PNI between the CRT responders and non-responders (44.2±7.0 vs. 43.7±6.0, p=0.682). However, the prevalence of positive ΔPNI was significantly higher in the CRT responders than in the non-responders (70.1% vs. 50.0%, p=0.025).

Discussion

There were several important findings in the present study. First, in the Kaplan-Meier analysis, adverse events were significantly rarer in the positive ΔPNI group than in the negative ΔPNI group during the long follow-up. Second, in the positive ΔPNI group, significant improvements in echocardiographic data, including LVEDD, LVESD, LVEDV, LVESV, LVEF and TRPG, were observed after CRT-device implantation. However, in the negative ΔPNI group, no significant changes were detected in any echocardiographic parameters. Finally, there was a higher prevalence of CRT responders in the positive ΔPNI group than in the negative ΔPNI group. These results suggest that im-

Table 3. Echocardiographic Data before and 6 Months after CRT-device Implantation.

Echocardiographic data		Positive ΔPNI group (n=73)	Negative ΔPNI group (n=46)	p value
LVEDD (mm)	Baseline	62.9±8.7	62.4±10.1	0.795
	6 months	60.2±11.0*	60.7±11.6	
	Δ	-2.7±8.2	-1.6±6.9	0.498
LVESD (mm)	Baseline	54.7±10.5	54.0±11.8	0.719
	6 months	48.9±12.8*	51.6±13.1	
	Δ	-5.7±10.1	-2.3±7.8	0.059
LVEDV (mL)	Baseline	186.5±93.2	164.3±81.5	0.189
	6 months	149.8±71.8*	161.5±105.2	
	Δ	-36.6±75.3	-2.8±61.8	0.012
LVESV (mL)	Baseline	134.0±75.9	118.7±74.6	0.282
	6 months	98.2±62.3*	116.7±97.1	
	Δ	-35.8±61.7	-1.9±57.1	0.003
LVEF (%)	Baseline	31.0±11.8	30.9±9.4	0.949
	6 months	37.4±12.5*	33.9±14.0	
	Δ	6.3±13.0	3.0±12.7	0.174
TRPG (mmHg)	Baseline	27.5±10.9	29.8±13.8	0.440
	6 months	23.4±9.8*	28.7±10.8	
	Δ	-4.1±13.1	-1.0±13.9	0.348

*$p<0.05$ vs. Baseline.

CRT: cardiac resynchronization therapy, PNI: prognostic nutritional index, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVEF: left ventricular ejection fraction, TRPG: tricuspid regurgitation pressure gradient.
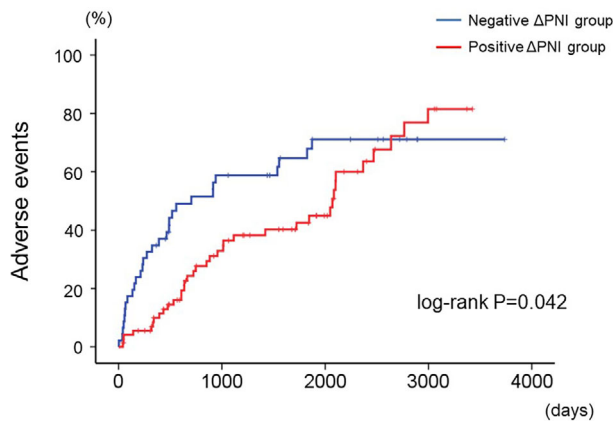

Figure 1. The risk of adverse events (re-hospitalization due to heart failure or all-cause death) in the positive and negative ΔPNI groups. The cumulative incidence curve with a log rank test showed that the positive ΔPNI group was associated with a lower rate of adverse events than the negative ΔPNI group. PNI: prognostic nutritional index

Figure 2. A comparison of the prevalence of the CRT responders between the positive and negative ΔPNI groups. CRT: cardiac resynchronization therapy, PNI: prognostic nutritional index

provement in the cardiac function after CRT-device implantation is correlated with increases in the PNI, resulting in favorable outcomes.

Functional response to CRT and change in the PNI

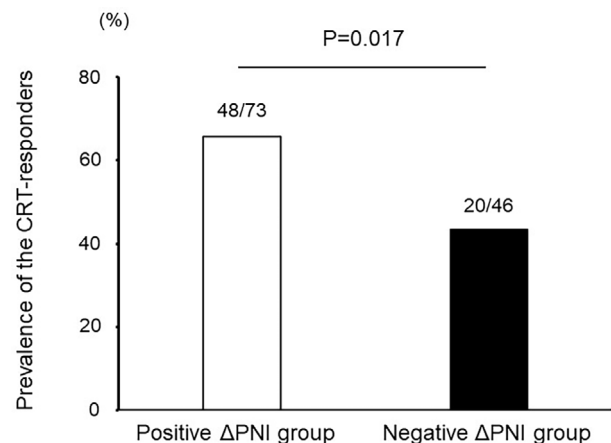The beneficial effects of CRT on the cardiac function and prognosis have been reported in patients with a CRT-device (1-3). In the present study, a higher prevalence of CRT responders was observed in the positive ΔPNI group than in the negative ΔPNI group. Intraventricular, atrioventricular, and interventricular synchronies can reportedly be improved by CRT (17). As a result of normalized synchrony by CRT, the cardiac output and LVEF are improved, and LV diastolic filling pressure is reduced, subsequently leading to a reduced LVESV, LVEDV, and pulmonary artery pres-

sure (17). Malnutrition is considered to be correlated with right ventricular dysfunction (8, 10). Right ventricular dysfunction can be caused by several factors, and that secondary to pulmonary hypertension due to left-sided HF is the most common type of dysfunction (18). In the current study, improvement in the LV function after CRT-device implantation in the positive ΔPNI group was supported by evidence of an increase in the LVEF as well as decreases in the LVEDD, LVESD, LVEDV, and LVESV.

In addition, a reduction in the TRPG after CRT-device implantation was found in the positive ΔPNI group. It is well known that the TRPG measured by echocardiography is a simple and useful indicator of pulmonary hypertension (19). The association of changes in the PNI with reverse remodeling and the prognosis has not been fully elucidated. Our findings suggest that a response to CRT causes LV reverse remodeling, improvements in cardiac output and congestion, and a subsequent improvement in the nutritional status, which lead to favorable outcomes.

The assessment of the PNI in patients with a CRT-device

In malnutrition and cardiac cachexia, neurohormonal alteration and systemic inflammation, characterized by a catabolic/anabolic imbalance, are considered to be associated with myocardial damage and cardiac overload (8, 20). Therefore, the assessment of the nutritional status is important for the clinical management of patients with HF. Chronic HF is commonly related to weight loss. However, the body mass index is sometimes not a good indicator of the nutritional status in patients with HF, as this measurement may be influenced by the presence of edema due to HF (21). In the present study, changes in the PNI were assessed to evaluate the cardiac function and clinical outcomes after CRT-device implantation. The PNI is calculated from the serum albumin concentrations and total lymphocyte count. Decreases in the rate of synthesis of albumin and lymphocyte proliferation are considered to be caused by both malnutrition and inflammation (22-24). Indeed, decreased and increased values of CRP after CRT-device implantation were found in the positive and negative ΔPNI groups, respectively, and the ΔCRP was significantly different between the two groups. In addition, recent studies have revealed that the PNI is also associated with hemoglobin, the renal function, sodium, BNP, and the right ventricular systolic pressure, leading to a poor prognosis (8, 10). In accordance with their findings, an increase in the hemoglobin level and decreases in the sodium and BNP levels after CRT-device implantation were detected in the positive ΔPNI group, whereas an increase in the creatinine level and a decrease in the hemoglobin level after CRT-device implantation were found in the negative ΔPNI group. Furthermore, in the positive ΔPNI group, there was a decrease in the total bilirubin level after CRT-device implantation. The total bilirubin level is reportedly correlated with right ventricular overload and adverse outcomes in patients with HF (25).

Therefore, in the Kaplan-Meier analysis, the positive ΔPNI group was associated with a lower prevalence of adverse events than the negative ΔPNI group during the long-term follow-up. In the present study, the PNI at baseline was lower in the positive ΔPNI group than in the negative ΔPNI group. Although a low PNI is considered a simple predictor of a poor prognosis in patients with HF (9, 10), our study findings indicate that increases in the PNI after CRT-device implantation are related to favorable outcomes.

Limitations

Several limitations associated with the present study warrant mention. First, our sample size was relatively small. Second, the present results were obtained in a retrospective manner from a single institution. Finally, since we did not perform a multivariate Cox proportional hazard analysis due to the small sample size, the effect of differences, except for ΔPNI, in the clinical backgrounds between the groups might not be have been completely considered. We would perform another study to address these issues in the future.

Conclusion

Our study findings indicate that improvement in the cardiac function after CRT-device implantation is associated with increases in the PNI, which lead to favorable outcomes. The evaluation of the nutritional status, as assessed by changes in the PNI, is important for the clinical management of HF patients with a CRT-device.

The authors state that they have no Conflict of Interest (COI).

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