

Original Article

Clinical value of serum NT-proBNP level in the diagnosis of rheumatoid arthritis with cardiac insufficiency

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Received December 6, 2019; Accepted January 13, 2020; Epub July 15, 2020; Published July 30, 2020

Abstract: Objective: To investigate the clinical value of serum sputum end-type natriuretic peptide (NT-proBNP) level in the diagnosis of rheumatoid arthritis (RA) with cardiac insufficiency. Method: A total of 419 patients with RA and cardiac insufficiency admitted to Rui Jin Hospital affiliated to Shanghai Jiao Tong University School of Medicine from June 2016 to June 2017 were included. (1) Analysis of the correlation between the patients' basic characteristics, such as age and gender, and the NT-proBNP level; (2) Analysis of the correlation between the NT-proBNP level and cardiac function indexes, left ventricular ejection fraction (LVEF) and TDI-Tei; (3) Analysis of the correlation between the NT-proBNP level and Rheumatoid related factors, such as Anti-citrullinated fibrinogen (ACF) and anti-cyclic citrullinated peptide (CCP resistance); (4) The application of NT-proBNP level in the prognostic evaluation of patients with RA complicated with cardiac insufficiency within 2 years for cardiovascular incidence and mortality. Results: The 419 patients were divided into high NT-proBNP group and low NT-proBNP group with 4647 pg/ml as the boundary. Between the two groups, there were no statistically significant differences in age, gender, BMI and vascular risk factors, but in the high NT-proBNP group, cardiac function ($P < 0.05$) and rheumatoid factor levels ($P < 0.05$) were elevated as compared with the low NT-proBNP group. The area under the ROC curve of cardiovascular events in patients with CRS, as predicted according to the NT-proBNP level, was 0.838, while the sensitivity and specificity were 88.9% and 75.0%, respectively. The NT-proBNP level of 4647 pg/ml was used as the cut-off value to establish the incidence curve of cardiovascular events for patients at different levels of NT-proBNP during the 2-year follow-up period by Kaplan-Meier method, and the Log-rank value was 51.673 ($P < 0.001$). Conclusion: The circulating level of NT-proBNP is a prognostic biomarker for patients with RA with cardiac insufficiency.

Keywords: NT-proBNP, cardiac insufficiency, rheumatoid arthritis, prognosis, biological indicators

Introduction

Rheumatoid arthritis (RA) is a common chronic arthritic lesion in the elderly, and complicated with multiple other symptoms involving other parts in addition to joints in serious cases, of which, the impairment of the cardiovascular system accounts for the most in chronic cardiac insufficiency [1]. According to related studies, 67% of the RA patients are suffering from impairment of the cardiovascular system concurrently, including congestive heart failure and ischemic heart disease which are more common, while 43% of the cases may develop to chronic cardiac insufficiency and die [2, 3]. Therefore, the early diagnosis of chronic cardiac insufficiency is vital to the control of arthri-

tis. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a major component secreted by the heart, and a biomarker reflecting the impairment of cardiac functions [3, 4]. Related studies have revealed that in patients with impaired cardiac muscles, the increase of NT-proBNP rises [5, 6]. Matusik pointed out in his study that the level of NT-proBNP kept on rising after ventricular damage, which can be referred when judging the severity of hemodynamic dysfunction in patients with heart disease. However, gender, age and other factors severely affect the serum concentration of NT-proBNP [7]. Vilela concluded through his study that the changes in metabolic level may also severely affect NT-proBNP level [8], while Lazurova held the ground that patients with RA

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are also suffering from cardiac damage, leading to the release of NT-proBNP by cardiac muscle cells and accumulation, and the rise of NT-proBNP level so that the prognosis effect of patients with chronic arthritis and cardiac insufficiency is effected [9].

In this study, patients with chronic arthritis and chronic cardiac insufficiency were detected for serum NT-proBNP level to establish (1) the impact of basic characteristics, such as age and gender, on NT-proBNP level; (2) the correlation between the cardiac function and NT-proBNP level; (3) the correlation between rheumatoid related factors and NT-proBNP level; (4) the application of NT-proBNP level in the prognostic evaluation of patients with RA and chronic cardiac insufficiency. The NT-proBNP level provides new references for the early diagnosis and prognosis of patients with RA and chronic cardiac insufficiency.

Materials and methods

Study objects

In this study, patients with RA and cardiac insufficiency admitted to Rui Jin Hospital affiliated to Shanghai Jiao Tong University School of Medicine from June 2016 to June 2017 were included. The study has been approved by the local ethics committee. All patients have signed the informed consent.

All patients satisfied following inclusion and exclusion criteria. Inclusion criteria: 1) The patients have been diagnosed with RA [10]; 2) The patients were concurrently suffering from chronic cardiac insufficiency with NYHA cardiac functional grading above grade II; 3) The LVEF \leq 45%; 4) All patients understood and agreed to cooperate with the clinical study by issuing their informed consent.

Exclusion criteria: 1) Patients with diseases in liver and kidney, requiring long-term hemodialysis; 2) Patients with a medical history of auricular fibrillation concurrently; 3) Patients with malignant arrhythmia concurrently when attacked.

Observation indicators

The demographic data (age, gender, marital status, smoking or not), cardiac function score, LDL, blood pressure, heart rate, creatinine, glo-

merular filtration rate, blood N-Terminal-pro brain natriuretic peptide (NT-proBNP), ACF, and anti-CCP level detection.

Measurement method of NT-proBNP indicators

NT-proBNP level was measured by chemiluminescence [11] in the range of 1 and 25000 pg/ml. With 4647 pg/ml as the cut-off value [12], patients were divided into the low NT-proBNP group (\leq 4647 pg/ml) and high NT-proBNP group ($>$ 4647 pg/ml).

Evaluation results and follow-up

Major observation indicators include CV and all-cause mortality, and secondary observation indicators are statistical analysis of the association between NT-proBNP level and patients' age, gender, cardiac function index (CFI), and rheumatoid related factors (ACF, and CCP resistance). Patients selected were tested for blood NT-proBNP level, ACF, and CCP resistance levels, and followed up every half a year to record any cardiovascular event (coronary disease, cerebrovascular disease, elevation of blood pressure, etc.) and deaths due to angiocardiopathy. The follow-up lasted 2 years.

Statistical analysis

Continuous variables are expressed as SD, compared by student t or median \pm quartile if normally distributed, or by Mann-Whitney U if not. Kolmogorov-Smirnov test was applied to evaluate the normality of data distribution. The correlation between data was evaluated by Pearson related coefficients. For monofactor analysis, logistic regression analysis was employed. ROCs were mapped and the area under curve (AUC) was evaluated by Simpson. The prognostic value of CRS patients was evaluated according to the different levels of NT-proBNP, and the sensitivity and specificity were quantitatively calculated at various points. During the follow-up, the incidence of cardiovascular events was studied by the Kaplan-Meier method. For all statistical comparisons, significance was defined as $P < 0.05$.

Results

General characteristics of patients

There were 419 patients in the study, of which, 180 had a NT-proBNP under 4647 pg/ml and

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Table 1. General characteristic of patients

Parameter	High NT-proBNP group (n=239)	Low NT-proBNP group (n=180)	P
Men/women (%)	102/137	58/122	0.672
Age (years), mean (range)	65.2±3.77	66.76±3.87	0.712
Married/unmarried (%)	209/30	155/25	0.671
BMI (kg/m ²)	26.8	27.2	0.565
Smoking (%)	75	69	0.732
NYHA (n)			
NYHA III	167	142	0.31
NYHA IV	72	38	0.33
LDL (mmol/l)	3.5	3.4	0.176
Blood pressure (mmhg)	127/88	129/86	0.455
Heart rate (1/min)	72	77	0.135
Creatinine (μmol/L)	334.13	217.77	0.021*
GFR-MDRD (ml/s)	21.38	34.51	0.031*
Incidence of cardiovascular events (%)	43.2	7.2	0.001*
Cardiogenic death (case)	27	3	0.003*

Note: Compared with low NT-proBNP group, *P<0.05. NT-proBNP: N-terminal B-type natriuretic peptide; BMI: body mass index; NYHA: New York Heart Association; LDL: low-density lipoprotein; GFR-MDRD: glomerular filtration rate.

Table 2. Correlation between NT-proBNP levels and cardiac function

	LVEF	TDI-Tei
Low NT-proBNP (n=239)	57.21±0.13	0.35±0.02
High NT-proBNP (n=180)	42.11±0.11	0.49±0.03
t	3.32	2.15
P	0.019*	0.023*

Note: Compared with low NT-proBNP group, *P<0.05. NT-proBNP: N-terminal B-type natriuretic peptide.

239 above 4647 pg/ml. No significant difference was observed between the two groups for general baseline data (such as age distribution, gender and BMI), blood lipid and pressure (**Table 1**).

Correlation between NT-proBNP level and cardiac function

The two groups' LVEF and TDI-Tei were statistically analyzed. The LVEF of the low NT-proBNP group was 57.21±0.13, which was higher than that of 42.11±0.11 in the high NT-proBNP group (P<0.05). The TDI-Tei of the low NT-proBNP group was 0.35±0.02, which was lower than that of 0.49±0.03 in the high NT-proBNP group (P<0.05) (**Table 2**).

Correlation between NT-proBNP and rheumatoid factor ACF, and CCP resistance

The two groups were analyzed for rheumatoid factor ACF, and CCP resistance. The ACF of the

Table 3. Correlation between NT-proBNP and rheumatoid factor ACF, CCP resistance

	ACF	CCP resistance
Low NT-proBNP	0.209±0.001	0.024±0.001
High NT-proBNP	0.921±0.001	0.002±0.001
t	2.11	5.22
P	0.013*	0.021*

Note: Compared with low NT-proBNP group, *P<0.05. NT-proBNP: N-terminal B-type natriuretic peptide.

low NT-proBNP group was 0.209±0.001, which was lower than that of 0.921±0.001 in the high NT-proBNP group (P<0.05). The CCP resistance of the low NT-proBNP group was 0.024±0.001, which was higher than that of 0.002±0.001 in the high NT-proBNP group (P<0.05). Compared with the low NT-proBNP, the high NT-proBNP group experienced rising in ACF and reduction in CCP resistance (**Table 3**).

2-year incidence of cardiovascular events was predicted based on the NT-proBNP level

Cured patients were followed up for 2 years, and the results indicated higher incidence of cardiovascular diseases in the high NT-proBNP. The AUC of ROC for 2-year cardiovascular events was 0.756 and the 95% CI was between 0.733 and 0.990 (P<0.01). When the NT-proBNP was 4647 pg/ml, the specificity and sensitivity of cardiovascular events in the 2 years were predicted to be 76.0% and 87.2%.

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Table 4. NT-proBNP levels predict the incidence of cardiovascular events in 2 years of CRS patients

	Cardiovascular event rate (%)
Low NT-proBNP	37
High NT-proBNP	66
t	4.12
P	0.011*

Note: Compared with low NT-proBNP group, * $P < 0.05$. NT-proBNP: N-terminal B-type natriuretic peptide.

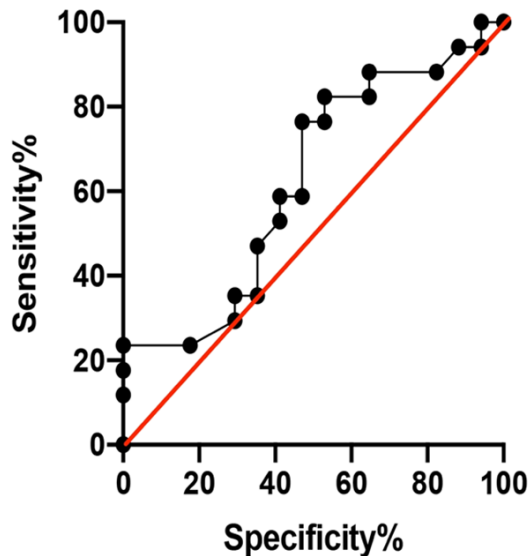


Figure 1. N-terminal B-type natriuretic peptide level predicts ROC curve of cardiovascular events in patients with heart failure within 2 years. The NT-proBNP level predicts the ROC curve of cardiovascular events in 2 years of CRS patients: NT-proBNP levels predict the area under the ROC curve for cardiovascular events within 2 years of CRS patients is 0.838 (95% confidence interval 0.773~0.904), $P < 0.01$. When the NT-proBNP level was 4647 pg/ml, the sensitivity and specificity of predicting cardiovascular events in 2 years were 88.9% and 75.0%, respectively.

With the NT-proBNP of 4647 pg/ml as the grouping criteria, the incidence of nil cardiovascular events in patients at various levels was analyzed, and found that during the follow-up, the group with NT-proBNP ≤ 4647 pg/ml had a curve of nil cardiovascular events significantly higher than the group with NT-proBNP > 4647 pg/ml. The calculated Log-rank value was 51.673 ($P < 0.001$). The 2-year survival was 37.1% for patients with NT-proBNP > 4647 pg/ml and 92.0% for patients with NT-proBNP ≤ 4647 pg/ml ($P < 0.05$) (Table 4 and Figure 1).

Table 5. NT-proBNP levels predict 2-year patient survival

	2-year patient survival (%)
Low NT-proBNP	89
High NT-proBNP	47
t	3.27
P	0.022*

Note: Compared with low NT-proBNP group, * $P < 0.05$. NT-proBNP: N-terminal B-type natriuretic peptide.

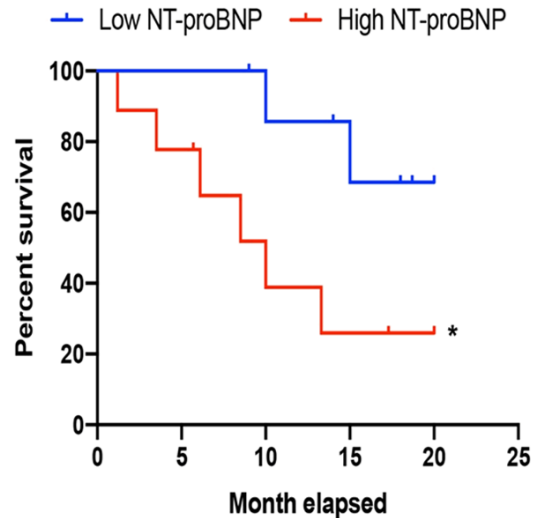


Figure 2. Cardiac vascular events during follow-up at different NT-proBNP levels. Survival rate at 2 years follow-up for patients with different NT-proBNP levels by Kaplan-Meier method with NT-proBNP levels of 4647 pg/ml. The 2-year survival rate was 37.1% in the NT-proBNP > 4647 pg/ml group and 92.0% in the NT-proBNP ≤ 4647 pg/ml group. The difference was statistically significant (* $P < 0.05$).

2-year survival of patients based on NT-proBNP level

According to statistical analysis of the 2-year survival of both groups, the high NT-proBNP group yielded lower results (Table 5).

During the follow-up, the incidence of cardiovascular events in patients with different NT-proBNP levels was as follows (Figure 2).

The Kaplan-Meier method was adopted to analyze the survival of patients at different NT-proBNP levels during the 2-year follow up. Patients were divided into two groups with the NT-proBNP level of 4647 pg/ml as the cut-off value. The group with NT-proBNP ≤ 4647 pg/ml had a follow-up survival curve obviously higher

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than the group with NT-proBNP >4647 pg/ml. The Log-rank value was 51.673 ($P<0.001$). The 2-year survival was 47% in the group with NT-proBNP >4647 pg/ml and 89.0% in the group with NT-proBNP \leq 4647 pg/ml ($P<0.05$).

Discussion

General information of b-type natriuretic peptide

NT-proBNP is a cardiac neurohormone secreted by heart chambers under the effects of dragging cardiac muscle cells, rising wall tension or other factors resulting in myocardial stress [13]. In a previous study, Hall proposed that the NT-proBNP level may have a relation with the patients' age and gender [14], but Corrao believed that there was no obvious statistical difference between patients with chronic rheumatic arthritis [15]. Similarly, the results of the present study also revealed no significant correlation between the NT-proBNP level and patients' age and gender. The possible reason may be that most of the patients with rheumatic arthritis and chronic cardiac insufficiency were female at an age over 60. The narrow age distribution accounted for little obvious difference. According to the study of Hohl, it is believed that the basic metabolic rate may affect the NT-proBNP level [16]. However, the results of the present study showed no significant difference between the two groups in terms of BMI. Therefore, little impact was imposed on the NT-proBNP level. In addition, in this study, patients' cardiovascular risk factors were analyzed, including smoking, blood lipid and pressure, which had no significant statistical correlation with the NT-proBNP level, a result similar to the finding in the related studies by Hohl. Henceforth, the NT-proBNP level can be taken as a diagnostic indicator for patients with RA and cardiac insufficiency.

With cardiac functions

Through statistics of existing clinical studies, it is learned that in the early stage of cardiac insufficiency, the NT-proBNP level rises, which can be used as a valuable evidence to predict short- and long-term mortality [17]. The combination of NT-proBNP, LVEL and TDI-Tei can reflect the overall cardiac functions as a predictive indicator for the death of patients with acute or chronic heart failure [18]. Santema et

al. found in their study that the NT-proBNP has a close relationship with LVEF, and can be relied on to judge the overall cardiac functions [19]. According to the study results of Zhou et al., compared with other parameters, the NT-proBNP and TDI-Tei can better predict the short- and long-term prognosis of patients with acute heart failure [20]. In the present study, significantly lower LVEF and TDI-Tei were found in the high NT-proBNP group as compared with the low NT-proBNP group ($P<0.05$). The possible reason might be that in the high NT-proBNP group, patients' cardiac volume load and cardiac stress increased, further impairing their cardiac functions and leading to more NT-proBNP released by the cardiac muscle cells.

With rheumatic factors

Existing study results have revealed that, RA-related factors have a risk of impacting the development of angiocardiopathy. In the established RA patients, Yang applied electron beam scanning to detect more common and serious coronary artery calcification cases than early RA patients and healthy groups [21]. In related clinical studies, Schnorbach et al. certified that the higher patients' ACF is, the higher the corresponding NT-proBNP is, and more severe the patients' cardiac damage is [22]. In the control study of cases, Zhang found that in patients without RA, ACF and CCP resistance rose along with NT-proBNP, corresponding to more severe cardiac function damage [23]. During this study, correlation was found between patients' rheumatoid factor level and NT-proBNP. The underlying reason shall be that the patients with rheumatoid diseases were concurrently suffering from problems such as myocardial damage. The damaged cardiac muscle cells produced large amount of NT-proBNP, which accounted for the rising of NT-proBNP in patients.

With cardiovascular events and survival

A large number of clinical studies have testified that NT-proBNP can be used as a predictive factor for prognosis. The method has been applied in the diagnosis of heart failure [24]. However, further studies are required on the prognosis of patients with RA and cardiac insufficiency [25]. In the present study, with NT-proBNP of 4647 pg/ml as the cut-off value, a ROC analysis was conducted, in which, the

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AUC of RA patients suffering from cardiovascular events in 2 years was 0.838, the sensitivity and specificity were 88.9% and 75.0% respectively. Analysis of patients at different levels of NT-proBNP confirmed that the group with NT-proBNP ≤ 4647 pg/ml had better prognosis, and a 2-year survival 1.89 times of the group with NT-proBNP >4647 pg/ml.

Study limitations

This study only included 419 patients, which is insufficient. Future studies shall be based on larger sample size. Therefore, as most of the included patients were at a senior age with high cardiovascular risk, with NT-proBNP =4647 pg/ml as the boundary, this study excluded the impact of other factors such as age on cardiovascular risk. In addition, restricted by the short follow-up period, only preliminary results were harvested. In the future, subsequent follow-up studies shall be necessary.

Conclusion

Serum NT-proBNP level can be used to predict the indicators such as cardiac functions and active stage of rheumatoid in patients with RA and cardiac insufficiency, and their subsequent cardiovascular incidents, providing a reference for their prognosis and 2-year survival.

Acknowledgements

This work was supported by National Natural Science Foundation of China, Project Approval No.: 81772372.

Disclosure of conflict of interest

None.

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