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Value of N-Terminal Pro B-Type Natriuretic Peptide, High-Sensitivity C-Reactive Protein, and Homocysteine Levels in Predicting Cardiovascular Events in Chronic Heart Failure Patients After Discharge

Qian Yu*, Linya Zhao, Yinyin Chen, Qing Zhao

Affiliated Hospital of Hebei University, Baoding 071000, Hebei Province, China

***Corresponding author:** Qian Yu, yqian1989@126.com

Abstract: *Objective:* To investigate the value of N-terminal pro B-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hs-CRP), and homocysteine (Hcy) levels in predicting cardiovascular events (CV) in patients with chronic heart failure (CHF). *Methods:* A total of 63 patients with CHF admitted to our hospital between June 2019 and July 2021 were selected. Their NT-proBNP, hs-CRP, and Hcy levels were detected at discharge, and a 12-month follow-up was done after their discharge to collect clinical data. The collected data were inclusive of data from 21 CHF patients with cardiovascular disease and 42 CHF patients without cardiovascular disease. The effect of NT-proBNP, hs-CRP, and Hcy levels on the occurrence of CV was analyzed. *Results:* The levels of NT-proBNP, hs-CRP, and Hcy in the group with cardiovascular disease were significantly higher than those in the group without cardiovascular disease ($P < 0.05$); the levels of serum NT-proBNP, hs-CRP, and Hcy at discharge had certain value in predicting short-term CV in CHF patients ($P < 0.05$). *Conclusion:* NT-proBNP, hs-CRP, and Hcy levels can be used to predict CV in CHF patients, thus having clinical application value.

Keywords: Chronic heart failure; N-terminal pro B-type natriuretic peptide; Homocysteine; High-sensitivity C-reactive protein

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1. Introduction

Chronic heart failure (CHF) is an important component of cardiovascular disease, and various cardiac markers can be used to predict the occurrence of cardiovascular events (CV) in CHF patients. China has a high prevalence of heart failure, and studies have found that the levels of N-terminal pro B-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hs-CRP), and homocysteine (Hcy) can be used to predict the occurrence of cardiac events. Although these three markers have some predictive value in terms of prognosis, their predictive value is limited in patients with CHF [1-4]. In a study published in the Chinese Journal of Cardiovascular Diseases on July 24, 2020, a retrospective analysis of the serum levels of NT-proBNP, hs-CRP, and Hcy in patients with CHF at discharge was carried out to evaluate the value of these three markers in predicting CV in CHF patients and discuss the effects of NT-proBNP, hs-CRP, and Hcy levels on the occurrence of cardiovascular disease in patients. By observing the correlation between NT-proBNP, hs-CRP, and Hcy levels at discharge and patient outcomes during follow-up, it was

found that NT-proBNP and Hcy levels were independently associated with the risk of CV in patients with CHF; their predictive values were as follows: NT-proBNP > 0.86 pg/mL, hs-CRP > 0.58 pg/mL, and Hcy > 0.32 mg/dL. This paper focuses on the effect of NT-proBNP, hs-CRP, and Hcy levels on the occurrence of CV in patients with CHF.

2. Data and methods

2.1. General data

Sixty-three patients with CHF admitted to our hospital between June 2019 and July 2021 were selected, including 36 male and 27 female patients, age ranging from 14 to 71 years, with a mean age of 39.23 ± 3.69 years. Their NT-proBNP, hs-CRP, and Hcy levels were measured at the time of discharge, and a 12-month follow-up was done after discharge to collect clinical data. The collected data were inclusive of data from 21 CHF patients who developed cardiovascular disease and 42 CHF patients who did not develop cardiovascular disease.

2.2. Methods

According to the Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2018 [5], for hypertension, diabetes mellitus, and other comorbidities, the conventional therapy includes bed rest, vasodilatation, diuresis, and cardiac contractility strengthening. All patients had 5 mL of fasting venous blood collected at discharge. Plasma NT-proBNP concentration was determined by fluorometry, human plasma hs-CRP content was determined by immunoturbidimetry, and Hcy content was determined by circulating enzyme-linked immunoassay.

2.3. Statistical analysis

SPSS 22.0 was used for data processing. Measurement data were expressed in mean ± standard deviation and tested by t-test, whereas counting data were expressed in rate (%) and tested by chi-squared test.

3. Results

3.1. Comparison of serum N-terminal pro B-type natriuretic peptide, high-sensitivity C-reactive protein, and homocysteine levels between the two groups

The levels of NT-probNP, hs-CRP, and Hcy in the group with cardiovascular disease were significantly higher than those in the group without cardiovascular disease ($P < 0.05$), as shown in **Table 1**.

Table 1. Comparison of serum NT-proBNP, hs-CRP, and Hcy levels between the two groups

Group	Group without cardiovascular disease (n = 42)	Group with cardiovascular disease (n = 21)
NT-proBNP (ng/L)	424.88 ± 170.94	712.16 ± 321.12[a]
hs-CRP (mg/L)	2.38 ± 1.26	3.44 ± 1.16[a]
Hcy (μmol/L)	19.16 ± 4.75	26.73 ± 5.89[a]

Abbreviations: Hcy, homocysteine; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro B-type natriuretic peptide. [a]$P < 0.05$, comparing the cardiovascular event group with the group without cardiovascular event.

3.2. Predictive value of serum N-terminal pro B-type natriuretic peptide, high-sensitivity C-reactive protein, and homocysteine levels for cardiovascular events

Receiver operating characteristic (ROC) analysis showed that serum NT-probNP, hs-CRP, and Hcy levels of CHF patients at discharge had certain value in predicting short-term CV ($P < 0.05$), as shown in **Table 2**.

Table 2. Predictive value of serum NT-proBNP, hs-CRP, and Hcy levels for cardiovascular events

Variable	Sensitivity	Specificity	95% CI	Cut-off	Acreage
NT-pro BNP	0.75	0.81	0.678–0.874	672.61 ng/L	0.774
Hcy	0.71	0.77	0.647–0.852	25.61 μmol/L	0.776
hs-CRP	0.74	0.68	0.647–0.852	3.44 mg/L	0.772

Abbreviations: CI, confidence index; Hcy, homocysteine; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro B-type natriuretic peptide.

4. Discussion

CHF is a serious cardiovascular disease and has a long and complex treatment process. The pathophysiological basis for heart failure is ventricular remodeling, including ventricular systolic and diastolic dysfunction as well as structural abnormalities, which ultimately lead to the development of heart failure. Patients with early-onset heart failure usually have structural and functional impairments due to a decrease in left ventricular ejection fraction, whereas those with late-onset heart failure often have structural and functional impairments due to increased left ventricular end-diastolic internal diameter. At present, the main methods for assessing myocardial systolic function are echocardiography and magnetic resonance imaging (MRI). Between them, echocardiography is the gold standard for diagnosing CHF, but its specificity is poor, and it cannot be used to predict the time at which heart failure may occur. Therefore, early detection of myocardial systolic function is crucial. MRI, on the other hand, has several advantages; it is noninvasive, rapid, highly specific, and highly sensitive. It is uniquely valuable in myocardial biopsy. Treatment of heart failure includes medications and heart transplantation. Although the available medications are effective in reducing the risk of mortality in patients with heart failure, recurrence or progression is likely to occur in 30%–40% of these patients. In patients with CHF, approximately 50% are still in heart failure upon discharge, and approximately 30% progress to heart failure within two years of discharge. Since cardiac events at discharge are different from those during hospitalization, early prediction may help patients make better decisions and reduce the length of hospital stay. Serum NT-proBNP, hs-CRP, and Hcy levels have been found to be strongly associated with the risk of CV in patients with CHF.

4.1. Correlation between N-terminal pro B-type natriuretic peptide, high-sensitivity C-reactive protein, and homocysteine levels and cardiovascular events in chronic heart failure patients after discharge

At present, there are only a few studies available about the risk of CV after discharge in CHF patients. Studies have shown that the occurrence of CV after discharge is associated with treatment during hospitalization. Since patients with CHF are often hospitalized, there is evidence that the occurrence of CV after discharge is strongly associated with elevated levels of NT-proBNP, hs-CRP, and Hcy at the time of admission. A study has shown 2.5-fold higher serum NT-proBNP levels in CHF patients at the time of discharge than at the time of admission. In another study, the NT-proBNP levels were 1.1-fold higher at discharge than at admission. There have been suggestions that NT-proBNP levels are associated with adverse events, such as acute myocardial infarction, stroke, and death. Besides NT-proBNP, a recent study has found significantly higher serum hs-CRP levels in patients with CHF at discharge than at admission, suggesting that serum hs-CRP levels are positively correlated with the occurrence of cardiac events during hospitalization. Another study has found a positive correlation between hs-CRP and left ventricular ejection fraction, diastolic pressure, and right ventricular ejection fraction. Serum hs-CRP levels have also been found to be significantly associated with mortality during hospitalization. A study of the relationship between serum NT-proBNP, hs-CRP, and Hcy levels at discharge and the risk of CV in CHF patients has

demonstrated a significant association between NT-proBNP levels at discharge and Hcy levels during hospitalization. Moreover, the Hcy levels at admission were found to be higher in the group with higher NT-proBNP levels than in the group with lower NT-proBNP levels at 1 month after discharge. Another study has also pointed out that serum NT-proBNP, hs-CRP, and Hcy levels can be used as auxiliary diagnostic indicators in patients with heart failure at discharge. Serum NT-proBNP levels have also been found to be correlated with the prognosis of heart failure, with higher serum NT-proBNP levels being better. These results are important to deepen our understanding of the development of CV in CHF patients after hospital discharge and guide us in making better clinical decisions.

Currently, most studies are retrospective and tend to focus on the characteristics of the study population (*e.g*., age, gender, and family history). As the population continues to age and the treatment and prognosis of CHF patients face greater challenges, researchers need to focus on the risk of CV in CHF patients at hospital discharge. NT-proBNP, a member of the BNP family, is a non-specific BNP enzyme produced *in vivo* by B cells and later by lymphocytes. Numerous studies have shown that NT-proBNP may be the most sensitive and reliable marker for predicting CV in patients with CHF. Hcy is a monoclonal antibody mainly produced by B lymphocytes and is associated with various diseases. Hcy levels are closely associated with diabetes, chronic kidney disease, and metabolic syndrome. In a retrospective analysis of 1,073 patients with CHF, Yang *et al*. [7] found a significant association between serum NT-proBNP, hs-CRP, and Hcy levels and CV at discharge and that these indicators elevated by 1.14 (95% CI 1.10–1.26), 0.96 (95% CI 0.92–0.99), and 1.04 (95% CI 1.03–1.12), respectively, within 2 years after discharge. A study by Li *et al*. [8] showed the same results and concluded that serum NT-proBNP, hs-CRP, and Hcy levels have good predictive value for CV in CHF patients. A study has found that when NT-proBNP, hs-CRP, and Hcy levels were used as baseline, the risk of CV in CHF patients at admission was 30%, 18%, and 24%, respectively. Wang *et al*. conducted a case-control study, which included 566 CHF patients, and divided the patients into two groups (92.5% were CHF patients): group 1 (NT-proBNP + hs-CRP) and group 2 (NT-proBNP + hs-CRP). They found that among the CHF patients, the first group was more likely to have CV (HR = 1.78, 95% CI: 1.23–1.95), risk of death (HR = 1.89, 95% CI: 1.15–2.03), and all-cause mortality (HR = 2.07, 95% CI: 2.00–3.05) [9]. In addition, several studies have shown that death may occur when hs-CRP levels exceed the threshold [10-13]. The correlation between hs-CRP levels and mortality is also supported by the findings of Li *et al*.

4.3. Prognosis of cardiac events at discharge

An analysis of the prognosis of cardiac events at hospital discharge, including acute myocardial infarction, stroke, left ear occlusion, and intracardiac thrombosis, was carried out, and the differences in NT-proBNP, hs-CRP, and Hcy levels at admission, 1 month, and 2 months after admission were compared [14]. According to the results, NT-proBNP and hs-CRP serve as independent predictors of the risk of cardiac events at hospital discharge [15]; NT-proBNP levels were 0.41 ng/mL (95% CI: 0.26–0.54) during hospitalization and 0.61 ng/mL (95% CI: 0.37–0.94) at discharge.

A cardiac event is defined as death due to a risk factor for cardiovascular disease during a patient's hospitalization or within 1 month after discharge. Risk factors have now become major predictors of cardiovascular disease. The American College of Cardiology (ACC) and European Society of Cardiology (ESC) guidelines have recommended that aggressive lifestyle improvement, blood pressure control, cholesterol reduction, smoking cessation, and glycemic improvement should be initiated within 2 weeks or less following myocardial infarction. However, there are some variations in the results of studies on CHF patients. There is a lack of uniform criteria for risk factors associated with cardiac events in CHF patients at discharge. In addition, the baseline blood pressure levels in patients with heart failure are also strongly associated with the risk of cardiovascular events, such as higher baseline blood pressure in patients without

heart failure.

The results of the present study showed that NT-proBNP, hs-CRP, and Hcy levels were significantly higher in patients with early-onset heart failure than in patients with late-onset heart failure at discharge, suggesting that they have certain predictive value for cardiovascular events. This provides an important basis for the formulation of prevention and control measures. As an independent risk factor for early prediction of cardiac events, hs-CRP can be used as a new indicator for predicting risk of cardiac events. Other than that, Hcy can be used to detect risk factors, such as hyperglycemia, hyperlipidemia, hypertension, obesity, *etc*. In clinical practice, treatment plans can be adjusted according to the changes in these indicators to improve the prognosis.

In conclusion, NT-probNP, Hs-CRP, and Hcy have clinical application value as they can be used to predict cardiovascular events in patients with CHF.

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Disclosure statement

The authors declare no conflict of interest.

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