The Optimal Cut-off Value of Plasma BNP to Differentiate Heart Failure in the Emergency Department in Japanese Patients with Dyspnea


Objective In the emergency department, it is sometimes difficult to differentiate heart failure (HF) from other diseases (e.g., respiratory diseases) in patients who develop dyspnea. The plasma B-type natriuretic peptide (BNP) levels increase in patients with HF, and various levels are associated with specific New York Heart Association classes. Although the diagnosis of HF should not be made based only on the plasma BNP levels, the identification of a cut-off value for BNP to diagnose HF would be helpful.

Methods Patients admitted to the emergency department of our hospital with dyspnea between January 2010 and December 2011 were retrospectively reviewed. The patients whose estimated glomerular filtration rate was less than 30 mL/min/1.73 m² were excluded. Patients were divided into two groups; those with HF (n=131) and those without HF (n=138). The cut-off value for BNP was determined by the receiver-operating characteristic curve.

Results The area under the curve of this curve was 0.934. The optimal cut-off point for detection of HF was 234 pg/mL. The sensitivity and specificity were 87.0% and 85.5%, respectively. The fifth and 95th percentiles of the HF group were 132.2 and 2,420.8 pg/mL, respectively. Those of the non-HF group were 9.7 and 430.2 pg/mL, respectively.

Conclusion Our study suggests that a plasma BNP level cut-off value of 234 pg/mL can be used to detect HF in the emergency department.

Key words: B-type natriuretic peptide, diagnosis, respiratory disease, heart failure


Introduction

In the emergency department, it is sometimes difficult to differentiate heart failure (HF) from other diseases (e.g., respiratory diseases) in patients who present with dyspnea (1-4). The symptoms and physical findings of patients with HF are often non-specific or absent (1, 3, 5). In addition, a precise history cannot be obtained from critically-ill patients. Taking a chest X-ray at the bedside using a portable machine can be helpful, but it is often difficult to obtain an accurate diagnosis (6). Echocardiography might help to determine the cardiac condition; however, approximately 30-50% of patients with HF have either a normal or preserved systolic function (7-9).

B-type natriuretic peptide (BNP) is a peptide hormone secreted from the heart ventricle in response to volume or pressure overload. The plasma BNP levels increase in patients with HF, and various levels are associated with specific New York Heart Association (NYHA) classes (10).
BNP measurement in Japan (17).

Patients were divided into two groups: patients with HF and those without HF. The purpose of the present study was to diagnose or differentiate HF. Thus, if a patient had both pneumonia and HF, the patient was classified as having HF. Similarly, when a patient’s acute myocardial infarction (AMI) was complicated with HF, the patient was classified as having HF. The definition of HF was as follows: First, the physician in the emergency department diagnosed whether or not the patient had HF based on the Framingham criteria. Then based on the initial diagnosis, the patients were sent to a specific division for treatment (e.g. Division of Cardiology, Division of Respiratory Medicine). In the present study, the diagnosis was confirmed retrospectively after discharge based on the Framingham criteria by one of the investigators who was independent of the emergency department and was blinded to the plasma BNP levels. The following data (if appreciable) were also taken into consideration for confirming the diagnosis: physical findings, chest X-ray, laboratory findings other than the plasma BNP levels, ultrasound echocardiography, right heart catheterization, coronary angiography, left ventriculography, chest CT, pulmonary function tests, the patients’ response to specific treatments and the follow-up in an outpatient clinic.

The two groups were compared on the basis of age, sex and other laboratory findings. Continuous variables are expressed as the mean ± SD and were compared using unpaired t-tests. The plasma BNP levels were compared using the Mann-Whitney test. Categorical variables are expressed as percentages, and were compared using chi-square tests. Statistical significance was indicated by a value of p<0.05.

The cut-off value for BNP was determined by generating the receiver-operating characteristic (ROC) curve for the ability of the plasma BNP level to detect HF.

Thus, BNP is helpful for diagnosing and assessing the severity of HF as well as reflecting the prognosis of patients with HF (11, 12).

Although a diagnosis of HF should not be made based only on the plasma BNP levels, identifying a cut-off value for diagnosing HF would be helpful. However, there is currently no cut-off value available in Japan for use in the emergency room. Prompt and accurate treatment is necessary to obtain a better prognosis. Therefore, we carried out a study to determine the optimal cut-off value of plasma BNP levels for diagnosing HF.

**Materials and Methods**

The study protocol was approved by the Jikei University School of Medicine ethics committee (25-1111 7246).

Patients admitted to the emergency department of the Jikei University Kashiwa Hospital (a tertiary care center) with dyspnea from January 2010 through December 2011 were retrospectively reviewed. The patients who did not undergo a measurement of plasma BNP levels upon admission were excluded. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation (13) modified by the coefficient for Japanese patients (14): estimated GFR =194× Cr-1.094× age-0.287 (mL/min/1.73 m²). For female subjects, the estimated GFR was multiplied by a correction factor of 0.739. The patients with an estimated GFR <30 mL/min/1.73 m² were excluded from our study because low renal function significantly affects plasma BNP levels (15, 16). Plasma BNP levels were measured at the time of admission with a fluorescent enzyme immunoassay using two monoclonal antibodies for BNP (E Test TOSOH II, Tosoh Corporation, Tokyo, Japan). The E Test TOSHO II has previously been shown to be comparable to Shionoria BNP (the current gold standard for

![Figure 1. A histogram of the plasma BNP levels in heart failure and non-heart failure patients.](image-url)

<table>
<thead>
<tr>
<th>Plasma BNP level (pg/mL)</th>
<th>Non-HF (138)</th>
<th>HF (131)</th>
</tr>
</thead>
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<tr>
<td>6.25</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>12.5</td>
<td>2</td>
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<td>4</td>
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<tr>
<td>1,600</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>3,200</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>6.25</td>
<td>12.5</td>
<td>25</td>
<td>50</td>
<td>100</td>
<td>200</td>
</tr>
</tbody>
</table>

**Results**

The final diagnoses of the patients are shown in Table 1. A total of 269 consecutive patients with dyspnea were in-
including in this study. The study population consisted of 131 HF cases and 138 non-HF cases. Fig. 1 shows a histogram of the plasma BNP levels in the HF and non-HF groups. The characteristics of both groups were compared in Table 2. The mean age of the HF group was 72.8±12.2 years and that of the non-HF group was 70.0±12.3 years (Table 2). There was no significant difference between the groups. Males comprised 57.2% and 71.7% of the cases in the HF and non-HF groups, respectively (p=0.015). The body mass index (BMI) did not differ between the groups. The mean plasma BNP levels were higher in the HF group (870±775 pg/mL) than in the non-HF group (128±175) (p<0.001). The mean eGFR and serum hemoglobin (Hb) levels were lower in the HF group than in the non-HF group. In many patients with HF, renal function was disturbed at the time of admission (18). On the other hand, the mean CRP levels were higher in the non-HF group than in the HF group.

We examined the sensitivity and specificity of various cut-off values of BNP for predicting HF from the ROC curve (Fig. 2). The AUC of this curve was 0.934. We considered the BNP value with the shortest distance on the ROC curve as the optimal cut-off and determined that the optimal cut-off point to detect HF in patients with acute dyspnea was 234 pg/mL. The sensitivity and specificity of this cut-off were 87.0% and 85.5%, respectively. The cut-off values were identical when plasma BNP levels were analyzed on a log scale.

The sensitivity and specificity of these values suggest that plasma BNP levels are useful for the diagnosis of HF in cases presenting with dyspnea in the emergency setting. We also calculated the fifth and 95th percentiles of the HF and non-HF groups, which were 132.2 and 2,420.8 pg/mL, and 9.7 and 430.2 pg/mL, respectively, in the HF and non-HF groups. The sensitivity, specificity, positive predictive value and negative predictive value at various cut-off values of BNP are also shown in Table 3.

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### Table 2. The Characteristics of the Patients with and without Heart Failure.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>HF</th>
<th>Non-HF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>269</td>
<td>131</td>
<td>138</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.3±12.3</td>
<td>72.8±12.2</td>
<td>70.0±12.3</td>
<td>NS</td>
</tr>
<tr>
<td>Male (%)</td>
<td>64.6</td>
<td>57.2</td>
<td>71.7</td>
<td>0.015</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.5±4.0</td>
<td>22.4±3.6</td>
<td>22.5±4.4</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>138.2±29.4</td>
<td>143.2±31.4</td>
<td>133.3±26.5</td>
<td>0.007</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>97.6±26.9</td>
<td>100.2±28.7</td>
<td>95.1±24.9</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma BNP levels</td>
<td>489±667</td>
<td>870±775</td>
<td>128±175</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum Cr (mg/dL)</td>
<td>0.90±0.29</td>
<td>0.97±0.28</td>
<td>0.84±0.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>65.7±23.8</td>
<td>57.6±17.7</td>
<td>73.4±26.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum Hb (g/dL)</td>
<td>12.7±2.3</td>
<td>12.3±2.3</td>
<td>13.0±2.3</td>
<td>0.010</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>4.8±7.2</td>
<td>3.0±4.6</td>
<td>6.6±8.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Artificial Ventilation (%)</td>
<td>11.5</td>
<td>12.9</td>
<td>10.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

BMI: body mass index, BNP: B-type natriuretic peptide, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, Hb: hemoglobin, NS: not significant.

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### Table 3. The Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value for Various Cut-off Values of the BNP Level.

<table>
<thead>
<tr>
<th>BNP cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
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<tr>
<td>100 pg/mL</td>
<td>97.7%</td>
<td>64.4%</td>
<td>72.3%</td>
<td>96.7%</td>
</tr>
<tr>
<td>200 pg/mL</td>
<td>90.0%</td>
<td>79.7%</td>
<td>80.8%</td>
<td>89.4%</td>
</tr>
<tr>
<td>234 pg/mL</td>
<td>87.0%</td>
<td>85.5%</td>
<td>85.0%</td>
<td>87.4%</td>
</tr>
<tr>
<td>300 pg/mL</td>
<td>78.6%</td>
<td>89.8%</td>
<td>88.0%</td>
<td>81.5%</td>
</tr>
<tr>
<td>400 pg/mL</td>
<td>70.2%</td>
<td>94.2%</td>
<td>92.0%</td>
<td>76.9%</td>
</tr>
<tr>
<td>500 pg/mL</td>
<td>59.5%</td>
<td>97.1%</td>
<td>95.1%</td>
<td>71.6%</td>
</tr>
</tbody>
</table>

PPV: positive predictive value, NPV: negative predictive value.

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Figure 2. The receiver-operating characteristic curve for the ability of the plasma BNP level to detect heart failure.
Discussion

The plasma BNP levels in patients with heart failure

In patients with HF, the plasma BNP levels are useful for determining the diagnosis, and for evaluating the severity, response to treatment and prognosis. In the present study, the plasma BNP levels were much higher in the HF group than in the non-HF group. We determined the optimal cut-off value for diagnosing HF to be 234 pg/mL. Judging from the fifth percentile value of the HF group, HF can be ruled out when the plasma BNP levels are below 132 pg/mL. On the other hand, based on the 95th percentile value of the non-HF group, a non-HF disease can be considered unlikely when the plasma BNP levels are above 430 pg/mL. Taking these three BNP levels into account can therefore be useful for obtaining an accurate diagnosis of HF.

Echocardiography can be used to assess cardiac function and patients with disturbed systolic function may be diagnosed with HF based on echocardiography alone. On the other hand, patients without systolic dysfunction but with HF may be inaccurately diagnosed as non-HF cases based on the echocardiographic findings. Steg et al. (19) showed that an assessment of the BNP levels is superior to echocardiography for the diagnosis of HF on the basis of the ROC curve.

Plasma BNP levels in non-heart failure patients

In some patients without HF, plasma BNP levels were higher than the normal range. The non-HF patients whose plasma BNP levels were above the 95th percentile had pulmonary artery hypertension (n=2), pulmonary artery hypertension (n=2), septic shock (n=1) and AMI (n=1).

In patients with AMI, the plasma BNP levels increase in a biphasic manner regardless of the presence or absence of HF (20). Thus, the plasma BNP levels upon admission may not be the same as those after the onset of AMI. In the acute phase, BNP may be produced by myocardial necrosis, and/or local mechanical stress. On the other hand, in the subacute phase, BNP may be produced by infarct expansion and remodeling (20). Therefore, the levels in AMI patients vary. On the other hand, angina induces only small changes in the plasma BNP levels compared to AMI.

In patients with pulmonary artery hypertension, right ventricular failure is induced by volume overload, which might increase the BNP levels (21). The BNP gene is also expressed in the human right ventricle, suggesting that BNP is produced in both ventricles (22).

In some conditions, plasma BNP increases without a significant change in cardiac function; however, the mechanism of BNP increase remains to be investigated. In the present study, many of the patients with respiratory disease had pneumonia and interstitial pneumonia, which causes BNP levels to rise, and this increase in BNP correlates with the level of CRP (23). Our previous report showed that inflammation increases the plasma BNP level (24). In septic patients, the severity of the illness is the main determinant of the BNP level, rather than cardiac function (25).

Other extra-cardiac factors affecting the plasma BNP levels

Several factors are involved in the regulation of the plasma BNP levels (17, 24, 26, 27). The renal function is known to significantly affect the plasma BNP levels, therefore patients with an eGFR <30 ml/min/1.73 m² were excluded from the present study. Moreover, when renal function is disturbed, volume overload might affect the diagnosis of HF. Additionally, the plasma BNP levels are known to differ by gender; the plasma BNP levels of females are higher than those of males (17, 28). However, in the present study, there were no significant differences in the plasma BNP levels between males and females in either group (data not shown). We also did not find any relationship between age and the plasma BNP levels in either the HF or non-HF group (data not shown).

It is also known that the BNP levels are decreased in obese patients (27). This is discussed below.

Cut-off values in the previous studies

HF should not be diagnosed solely on the basis of the plasma BNP levels. However, measuring plasma BNP levels can help the diagnosis of HF. The cut-off values used to diagnose HF in previous studies of patients with acute dyspnea in the emergency department (3, 4, 29-35) are listed in Table 4. These studies showed that the plasma BNP level has high sensitivity, specificity and a high AUC to detect HF. However, the cut-off values varied among these studies. One of the reasons is that different populations were studied (19). Most of the previous studies were conducted in Western countries, except for one study from Korea. There has been no cut-off data established based on the clinical investigation of Japanese subjects. Our present cut-off value is comparable to the previous values (Table 4), and the relatively higher cut-off value in the present study might be partly explained by the race, lower BMI or older age of the Japanese population.

The Japanese Heart Failure Society (JHFS) presented the Attention for the medical care of HF using BNP or NT-proBNP statement (36). This statement set a cut-off value of 200 pg/mL for BNP, which indicates that treatment is necessary for probable HF. This cut-off value may have been a safety-sensitive one just before the worsening of HF. The present study focused on patients with dyspnea who came to a tertiary emergency medical facility due to worsening of symptoms. Moreover, the inflammatory status was relatively high in the present population (Table 2), and inflammation has been previously reported to increase the plasma BNP levels (24). The severity of HF and the presence of inflammation may explain the higher cut-off values of the BNP levels in the present study, therefore the present findings are in line with the cut-off described in the JHFS statement.
**Study limitations**

There were several potential limitations associated with this study. First, the sample size was small. Second, our hospital is a tertiary emergency medical facility. This means that almost all patients admitted to the emergency room are severely ill; mild cases are rare. The cut-off value is affected by the study population. In the present study, the mean plasma BNP levels were high even in the non-HF group (Table 2). Therefore, the cut-off value for a general hospital or outpatient clinic may be lower than the present study. Third, it is difficult to diagnose HF even after hospitalization. Even though some patients with pneumonia or other respiratory disease might have also had mild to moderate HF, we might not have detected it. Despite these limitations, this is the first study to find a cut-off value for the plasma BNP level in Japanese patients with acute dyspnea in an emergency department.

**Conclusion**

We found that measuring the plasma BNP levels is useful for diagnosing HF in the emergency department for patients presenting with acute dyspnea. The present study recommends using a plasma BNP level cut-off value of 234 pg/mL to detect HF in Japanese patients.

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

**References**


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**Table 4. The Cut-off Values of the Plasma BNP Level Reported in Previous Studies.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Symptom</th>
<th>Dept</th>
<th>n</th>
<th>Age</th>
<th>Cut-off</th>
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<tbody>
<tr>
<td>3</td>
<td>dyspnea</td>
<td>ED</td>
<td>250</td>
<td>63</td>
<td>80</td>
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<tr>
<td>4</td>
<td>acute dyspnea</td>
<td>ED</td>
<td>321</td>
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<td>29</td>
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<td>1,586</td>
<td>64</td>
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<tr>
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<td>67</td>
<td>300</td>
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<td>269</td>
<td>71</td>
<td><strong>234</strong></td>
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ED: emergency department, CPE: cardiogenic pulmonary edema, ALI: acute lung injury, HF: heart failure