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## ORIGINAL ARTICLE

## B-type natriuretic peptide in hypertensive crises: Diagnostic use in hypertensive urgencies and emergencies

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## KEYWORDS

B-type natriuretic peptide;  
Hypertensive emergency;  
Hypertensive urgency;  
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**Abstract** *Background:* It is not so easy to make a quick screening between hypertensive emergency (HE) and hypertensive urgency (HU), as it often requires sophisticated, complex and time consuming clinical, instrumental and diagnostic tests.

*Aim:* To address the role of B-type natriuretic peptide (BNP) in hypertension and how to use it to differentiate HE from HU to alleviate possible complications.

*Methods:* A total of 30 patients with rapid severe elevation of blood pressure (BP) admitted to the in-patient wards and critical care department, Cairo University, were included in a prospective, non-interventional study. On the basis of the clinical findings, patients were subdivided into two groups: *Group I:* 15 patients with HE with acute organ involvement and *group II:* 15 patients with HU without acute organ damage. Another 10 patients with chronic hypertension were taken as control group. BNP was measured in the blood at the time of admission based on the principle of competitive enzyme immunoassay.

*Results:* There was no significant correlation between the patients' age ( $58.5 \pm 12$ ) and BNP level ( $183.67 \pm 216.3$ ) ( $r = -0.17$ ,  $p = 0.3$ ) and also there was no significant difference in BNP blood level between males ( $223.35 \pm 179.2$ ) and females ( $131.77 \pm 255.2$ ) ( $p = 0.26$ ) and it was significantly higher in HE patients ( $324.33 \pm 233.16$ ) than HU patients ( $43 \pm 13.5$ ) and control group ( $8.13 \pm 5.8$ ) with  $p$ -value of  $<0.001$ . There was no significant difference in BNP level between HE patients with cardiac ( $313.33 \pm 179.6$ ) and neurological involvement ( $313.67 \pm 273.5$ ) ( $p = 0.8$ ), also, there was no significant difference in BNP level between patients presented with ischemic stroke ( $248.75 \pm 171$ ), hemorrhagic stroke ( $255 \pm 132$ ) and hypertensive encephalopathy (970) ( $p = 0.3$ ). Moreover, there was no significant correlation between BNP and systolic BP, diastolic BP, mean arterial pressure and pulse pressure in both studied patients and control groups

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( $p > 0.05$  in all). Receiver operator characteristic (ROC) curve was calculated for the use of BNP level as a diagnostic marker. The area under curve (AUC) for BNP as a diagnostic marker was 0.96.

**Conclusion:** During hypertensive crises BNP blood level determination could have a role as a diagnostic tool for the screening of HE and its evaluation is very useful in patients admitted with acute and rapid elevation of BP to limit target organ damage.

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## 12 Introduction

13 Hypertensive crisis is characterized by a rapid, often symptomatic rise in blood pressure (usually with diastolic blood pressure [DBP]  $> 120$  mmHg) in patients both with known or unknown arterial hypertension [1].

17 The pathophysiology of this clinical condition is mainly due to a sudden elevation of systemic vascular resistance [2], and the magnitude of the BP elevation is probably less important than the rapidity of the increase [3].

21 Hypertensive emergencies [HE] encompass a spectrum of clinical presentations where elevation of BP is complicated by evidence of impending or progressive target organ dysfunction [4]. The most important complications include ischemic stroke, hypertensive encephalopathy, hemorrhagic stroke and myocardial ischemia [5]. Morbidity and mortality depend on the extent of organ damage at presentation and on the degree of BP reduction [6].

29 On the other hand, Hypertensive urgency [HU] is a severe elevation in BP without progressive target organ dysfunction [4].

32 B-type natriuretic peptide (BNP), with the inactive fragment N-terminal pro hormone brain natriuretic peptide (NT-proBNP), is a peptide synthesized by atrial and ventricular cardiomyocytes, with a potent vasodilator, diuretic and natriuretic action; it decreases sympathetic outflow and inhibits vasopressin release [7].

38 The contribution of the measurement of BNP and NT-proBNP to the diagnosis and the prognosis of both acute heart failure and coronary syndromes has been well documented [8,9].

## 42 Aim of the work

43 There are not enough data on the potential diagnostic and prognostic role of BNP detection in distinguishing between HE and HU. In the following study we will try to address the role of BNP in hypertensive crises and how to use it to differentiate HE from HU to alleviate possible complications.

## 48 Patients and methods

### 49 Patients

50 The study protocol was approved by the local ethical committee. We prospectively enrolled thirty patients with rapid severe elevation of BP, admitted to the in-patient wards and critical care department, Cairo university hospitals; from August 2010 to February 2011. Informed consent was given by the patient or immediate relative (first degree). This study did not interfere with the medical decision toward the patient. No

invasive medical procedure is required by the protocol. Every patient received the optimum treatment that suits his medical condition.

### Exclusion criteria

61 Patients with age  $< 18$  and  $> 90$  years, heart failure, atrial fibrillation, primary pulmonary hypertension, chronic kidney impairment (serum creatinine level  $> 2.5$  mg/dl), liver cirrhosis, thyrotoxicosis, neoplasms, chest trauma or pregnancy, as these conditions may be associated with increase in BNP level.

### Inclusion criteria

67 Patients who did not meet any of the exclusion criteria were selected prospectively and included into the study.

69 On the basis of the clinical findings, patients were subdivided into two groups: *Group I*: 15 patients with HE due to the following acute organ involvement (heart; acute coronary syndrome or brain; hypertensive encephalopathy, acute cerebral ischemia, hemorrhagic stroke); diagnosis of stroke and myocardial ischemia was performed according to diagnostic criteria of international guidelines [10–12]; and *group II*: 15 patients with HU without acute organ damage. Another 10 patients with chronic hypertension were taken as control group.

78 All included patients were subjected to the following

### Full clinical evaluation

79 Including present history of the disease and past history of chronic hypertension and physical examination with special emphasis on blood pressure determination; systolic and diastolic BP were measured by a non invasive technique from left and right arms. The average of two consecutive readings taken 30 s apart was used.

### Laboratory investigations

87 **Routine labs.** CBC (complete blood count): Hemoglobin, Hematocrit, White blood cells and platelet count, Coagulation profile: PT (prothrombin time), PC (prothrombin concentration), INR and PTT (partial thromboplastin time), Liver function tests: ALT (Alanine aminotransferase), AST (Aspartate aminotransferase), BIL (bilirubin) total and direct and albumin, Kidney Function Tests: Na, K, Creatinine and Urea, Thyroid profile (freeT<sub>3</sub> freeT<sub>4</sub>, and TSH), Cardiac enzymes (CPK, LDH, CM-MB) and troponin.

96 These routine Labs were withdrawn on day 1 of the study.

97 **Specific labs.** BNP measurement: This was done by the use of BNP-32 (human) EIA kit provided by Phoenix pharmaceuticals, Inc. This kit is designed to detect a specific peptide and

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its related peptides based on the principle of competitive enzyme immunoassay.

**Blood sampling.** Blood samples were collected from patients on admission as follows: 7 ml of venous blood were drawn into tubes containing EDTA for anticoagulation and aprotinin (protease inhibitor), each tube was gently rocked for several times immediately after collection of blood to prevent blood clotting and inhibit the activity of proteases, then centrifuged at 1600g for 15 min at 4 °C and plasma was collected in eppendorf tubes and kept at -70 °C till analysis.

**Principle of the assay.** The immunoplate in the kit is precoated with secondary antibody and the non specific binding sites are blocked. The secondary antibody can bind to the Fc fragment of the primary antibody (peptide antibody) whose Fab fragment will be competitively bound by both biotinylated peptide and peptide standard or targeted peptide in samples. The biotinylated peptide interacts with streptavidin-horse radish peroxidase (SA-HRP) which catalyzes the substrate solution. The intensity of the yellow is directly proportional to the amount of biotinylated peptide-SA-HRP complex but inversely proportional to the amount of the peptide in standard solutions or samples. This is due to the competitive binding of the biotinylated peptide with the standard peptide or samples to the peptide antibody (primary antibody). A standard curve of known concentration was established accordingly. The unknown concentration in samples can be determined by extrapolation to this standard curve.

**Calculation of results.** The standard curve was plotted on semi-log graph paper. It was constructed by plotting the known concentrations of standard peptide on the log scale and its corresponding OD reading on the linear scale. The standard curve shows an inverse relationship between peptide concentrations and the corresponding absorbance. As the standard concentration increases, the yellow color decreases, thereby reducing the OD absorbance.

#### Standard 12 leads ECG

To detect ischemia and to exclude atrial fibrillation.

#### Imaging studies

(a) **Echocardiography;** was done for all patients to assess the left ventricular function and to exclude pulmonary hypertension.

(b) **CT brain** was also performed to patients with cerebrovascular events when suggested by clinical condition.

#### Statistics

Data were statistically described in terms of range; mean and standard deviation (SD), median, frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups was done using unpaired student's *t*-test for independent samples when comparing 2 groups and Kruskal Wallis test with posthoc multiple 2-group comparisons when comparing more than 2 groups. For comparing categorical data, Chi square ( $\chi^2$ ) test was performed. Exact test was used instead when the expected frequency is less than 5. Accuracy was

represented using the terms sensitivity and specificity. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off value for the studied diagnostic markers. Correlation between various variables was done using Spearman rank correlation equation for non normal variables. A probability value (*p*-value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2003 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

## Results

### Demographic and baseline clinical data at ICU admission Tables 1 and 2.

### BNP and baseline clinical characteristics

There was no statistically significant correlation between the age of the patients ( $58.5 \pm 12$ ) and BNP level ( $183.67 \pm 216.3$ ) ( $r = -0.17$ ,  $p = 0.3$ ). Also there was no significant difference in BNP level between males ( $223.35 \pm 179.2$ ) and females ( $131.77 \pm 255.2$ ) ( $p = 0.26$ ).

### BNP blood level between both HE and HU groups and control group

BNP was significantly higher in HE patients ( $324.33 \pm 233.16$ ) than HU patients ( $43 \pm 13.5$ ) and control ( $8.13 \pm 5.8$ ) groups with *p*-value of  $< 0.001$  (Table 3 and Fig. 1).

### BNP levels in hypertensive emergency group

There was no significant difference in BNP level between HE patients with cardiac ( $313.33 \pm 179.6$ ) and neurological involvement ( $313.67 \pm 273.5$ ) ( $p = 0.8$ ). There was no significant difference in BNP level between patients presented with ischemic stroke ( $248.75 \pm 171$ ), hemorrhagic stroke ( $255 \pm 132$ ) and hypertensive encephalopathy (970) ( $p = 0.3$ ).

### BNP levels in relation to blood pressure

1. There was no significant correlation between BNP and SBP in both studied patients and control groups ( $p > 0.05$ ) (Table 4).
2. There was no significant correlation between BNP and DBP in both studied patients and control groups ( $p > 0.05$ ) (Table 5).
3. There was no significant correlation between BNP and MAP in both studied patients and control groups ( $p > 0.05$ ) (Table 6).
4. There was no significant correlation between BNP and PP in studied patients and control groups ( $p > 0.05$ ) (Table 7).

### Diagnostic value of BNP

Receiver operator characteristic (ROC) curve was calculated for the use of BNP level as a diagnostic marker. The area un-

**Table 1** Demographic and clinical data of patients and controls in the study.

Characteristics	Patient's gp.	Control gp.
Age, mean ± SD in years (range)	58.5 ± 12 (29–74)	59.7 ± 8.96 (49–78)
Male:female sex (ratio)	17:13	6:4
Classification of the patients (N° of patients (%))		
Hypertensive urgency	15 (50%)	–
Hypertensive emergency	15 (50%)	–
Statistical distribution of target organ dysfunction		
Acute coronary syndrome	6 (40%)	–
Ischemic stroke	4 (26.7%)	–
Heamorrhagic stroke	4 (26.7%)	–
Hypertensive encephalopathy	1 (6.6%)	–

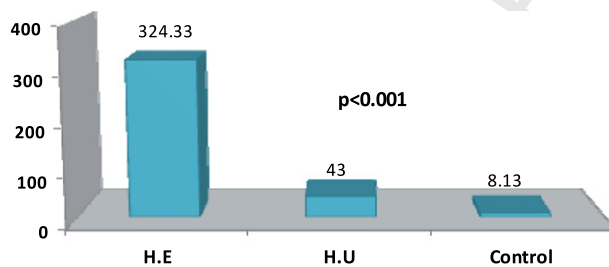
**Table 2** Characteristics of enrolled patients.

Variables	Total studied patients (n = 30)*	Hypertensive emergency(n = 15)	Hypertensive urgency(n = 15)	Control group
SBP (mmHg)	207 ± 18.7	211.3 ± 18.8	203 ± 18.3	140 ± 10.12
DBP (mmHg)	127.8 ± 7.9	129.7 ± 7.3	126 ± 6	84.5 ± 4.97
MAP (mmHg)	154 ± 9.9	156.6 ± 11	151.6 ± 8	104.89 ± 5.0
Pulse pressure (mmHg)	79 ± 16.3	81 ± 15	77 ± 17.7	56 ± 10.74
Serum creatinine (mg/dl)	1.05 ± 0.24	1.06 ± 0.23	1.04 ± 0.26	0.88 ± 34
DM (%)	46.6%	40%	53.3%	40%
Patients with no past history of HTN (%)	13.3%	6.7%	20%	–

Results are expressed as mean ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; DM, diabetes mellitus.

**Table 3** Comparison of BNP level between HE, HU and Control groups.

	Patients	No.	Mean	SD	p-Value
BNP	HE	15	324.33	233.16	<0.001
	HU	15	43	13.5	
	Control	10	8.13	5.8	



**Figure 1** BNP level in HE, HU and control groups.

der curve (AUC) for BNP as a diagnostic marker was 0.96 (Fig. 2).

**Discussion**

The natriuretic peptides have a vital counter regulatory role in clinical settings. Elevations of blood pressure and increased ventricular and vascular wall stress typically trigger an up

regulation of BNP gene expression [13]. Several studies showed that BNP appears to be released in response to increased wall stress. Ischemia can cause transient LV systolic and diastolic dysfunction [14,15].

There was no enough data on the potential diagnostic and prognostic role of BNP detection in distinguishing between HE and HU. Therefore, we tried in this study to assess the role of BNP in the course of hypertensive crisis, to evaluate the possible role of BNP in the differential diagnosis between HE and HU; and to investigate the relationship between BNP concentration and BP acute burden with consequent myocardial ischemia or brain damage.

Our study was conducted on 30 patients whose age ranged from 29 to 74 years (mean age 58.5 ± 12). We compared BNP in different ages and found that there is no significant correlation between BNP and age (p = 0.3 and r = -0.17).

This is in agreement with Ian Loke et al. [16], who found that plasma BNP is not influenced by age, in contrast to N-terminal pro-Atrial and N-terminal pro-B-type natriuretic peptides which showed positive correlation with 16% and 74% increase respectively in their levels for each 10 years of age. Other studies done by Redfield et al. [17], Wang et al. [18], and Di Somma et al. [19], found that BNP increased significantly with age and concluded that interpretation of BNP should include consideration of age.

Out of the thirty patients included, 17 were males (56.67%) and 13 were females (43.33%). On comparison of BNP level with both sexes we found no significant difference in BNP level between males (223.35 ± 179.2) and females (131.77 ± 255.2) (p = 0.257).

**Table 4** Correlation between SBP and BNP level in the studied population.

	SBP	BNP	r-Value	p-Value
HE	211.3	324.33	-0.22	0.43
HU	203	43	-0.18	0.5
Control	140.5	8.13	-0.11	0.74

**Table 5** Correlation between DBP and BNP level in the studied population.

	DBP	BNP	r-Value	p-Value
HE	129.67	324.33	-0.33	0.21
HU	126	43	-0.11	0.69
Control	84.5	8.13	-0.22	0.52

**Table 6** Correlation between MBP and BNP level in the studied population.

	MAP	BNP	r-Value	p-Value
HE	156.6	324.33	-0.24	0.38
HU	151.6	43	-0.22	0.41
Control	103.13	8.13	-0.25	0.48

**Table 7** Correlation between PP and BNP level in the studied population.

	PP	BNP	r-Value	p-Value
HE	81	324.33	-0.11	0.69
HU	77	43	-0.18	0.5
Control	56	8.13	0.08	0.81

246 This goes with the finding of Maisel et al. [20], who found  
 247 no significant difference in BNP level between males and  
 248 females. But it doesn't go with Ian Loke et al. [16], Redfield  
 249 et al. [17], and Wang et al. [18], who did their studies on  
 250 healthy volunteers and found that BNP level was higher in  
 251 females than in males, but they couldn't clearly explain the  
 252 physiologic basis for these sex related differences. Only the  
 253 stimulatory effect of female sex hormones on natriuretic

peptide gene expression and extra cardiac sources of natriuretic peptides within the female reproductive tract have been proposed [21].

In our study; patients were grouped on the basis of clinical findings into HE (15 pts) and HU (15 pts). HE patients were subdivided into 6 patients with acute coronary syndrome who accounted for 40% of HE cases; all of them presented with unstable angina and 9 pts with neurological involvement who accounted for 60% of HE cases and included 4 patients with ischemic stroke (26.7%), 4 patients with hemorrhagic stroke (26.7%), and only 1 patient with hypertensive encephalopathy (6.6%).

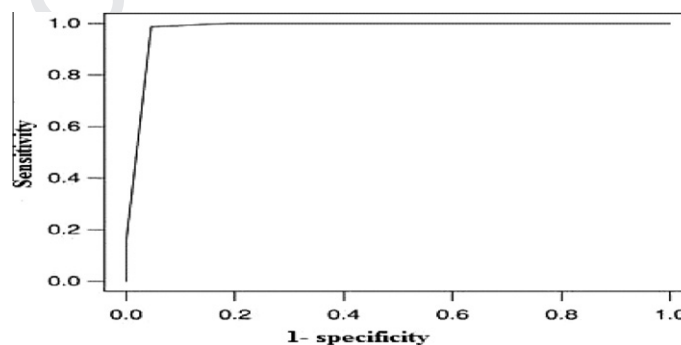
In our study BNP level was significantly higher in HE patients ( $324.33 \pm 233.16$ ) than HU patients ( $43 \pm 13.5$ ) ( $p < 0.01$ ) and it was higher in both groups than in the control group ( $8.13 \pm 5.8$ ) ( $p < 0.01$ ). But There was no significant difference in BNP level between HE patients with cardiac and neurological involvement ( $p = 0.8$ ) nor between patients presenting with ischemic stroke, hemorrhagic stroke and hypertensive encephalopathy ( $p = 0.3$ ).

As in our study; Di somma et al. [19] found that BNP blood level, in patients with highly elevated BP without organ damage, was significantly lower when compared with patients with HE. Moreover, the same study found that the value of BNP in the group of HU was roughly in the normal range as in young healthy adults (20–25 pg/ml) in other studies [18], and hence concluded that elevation of BP in HU does not cause an increase of BNP level [19]. This is in contradistinction with our findings that showed that BNP level was higher in both studied groups than in the control group.

In addition, the above study found that BNP in HE was greater in acute coronary syndrome subgroup when compared with neurological subgroup [19]; and this does not go with our study which found no significant difference in BNP level between both groups. This could be explained by the fact that our cases did not include myocardial infarction as in Di Somma et al. study.

In contrast to Di Somma and our study; Mäkikallio et al. [22] studied natriuretic peptides and mortality after stroke and made a comparison in BNP values between acute phases of stroke and acute myocardial infarction and found that stroke patients have equally high or even higher BNP plasma values than the acute myocardial infarction patients.

BNP levels in patients with acute coronary syndrome was studied by many authors as Kikuta et al. [23], who found that the plasma levels of BNP are increased in patients with unstable angina when compared with healthy control subjects and



**Figure 2** Diagnostic value of BNP.

those with stable angina. Also, Sabatine et al. [24] discovered that transient myocardial ischemia was associated with a rapid increase in BNP concentration which is secreted by undamaged cardiomyocytes in patients with acute coronary syndrome, and this increase was proportional to the severity of the ischemia.

Bassan et al. [25] analyzed the data of 631 patients diagnosed in the emergency room as myocardial infarction presented with chest pain and no ST-segment elevation on the ECG and they showed significantly higher BNP concentrations on admission compared to those with unstable angina. Patients with positive troponin values on admission demonstrated higher initial BNP concentrations compared to patients with negative initial results.

In aggregate the above findings suggest that transient ischemia increases wall stress and induce BNP synthesis and release in proportion to the degree of ischemic insults. The level of BNP may reflect the size or severity of ischemic insult even when myocardial necrosis has not occurred [26,27].

Di Somma et al. found that BNP level in neurological subgroup of HE was significantly greater than in HU group and it was supposed to be attributed to brain edema [19]. Moreover, other studies as Eguchi et al. [28], who studied the variation of BP and neurohumoral factors during the acute phase of stroke, found that BNP levels increased in the acute phase of stroke and that there was a positive correlation between BP levels and BNP levels. Also in the study of Tung et al. [29], on patients with subarachnoid hemorrhage, it was estimated that plasma BNP levels in patients with hypertension were higher than that in patients without hypertension.

Cakir et al. [30] found that plasma BNP levels in stroke patients with hypertension were higher than in stroke patients without hypertension and there was no relationship between plasma BNP levels and hemorrhage or infarction.

All the above studies done on BNP level in patients with neurological insults go hand in hand with our results of higher elevation of BNP level in hypertensive emergency cases with neurological involvement.

In our study; both studied groups with their subdivisions as well as in the control group there was no significant correlation between BNP level and systolic BP, diastolic BP, MAP and Pulse Pressure. Di Somma et al. [19] found no significant correlation between BNP level and SBP, DBP and MAP in HE and HU cases. While a statistical correlation was found between BNP level and PP in HU but not in HE studied patients. Yan Hua et al. [31] found that plasma BNP levels increase with increased PP, particularly PP > 7.98 kPa persons and this contradict findings in our study.

In Cakir et al. [30], study on BNP level in acute ischemic stroke and hypertension, they found positive correlation between plasma BNP levels and MAP.

In the study by Nakagawa et al. [32], it was found that although patients with intracranial hemorrhage had higher MAP levels than patients with ischemic stroke, the serum BNP levels were higher in patients with ischemic stroke than in those with intracranial hemorrhage. In the same study, it was shown that there was a weak positive correlation between the MAP levels and the BNP levels at the beginning of the ischemic stroke.

Jabeen et al. [33] and Kato et al. [34] found positive correlation between BNP level and SBP in patients with chronic hypertension. BNP value in Jabeen et al. study was  $27.06 \pm$

$6$  pg/ml in SBP  $\geq 140$  mmHg [33]. Also Jabeen et al. [33] and Jakubik et al. [35] found positive correlation between BNP level and DBP in patients with chronic hypertension. BNP value in Jabeen et al. study was  $33.55 \pm 8$  pg/ml in diastolic BP  $\geq 90$  mmHg [33].

In our study, BNP at the cutoff point of 90 pg/ml demonstrated a very high sensitivity and specificity in the diagnosis and differentiation between HE and HU. The predictive value of BNP concentration of  $\geq 90$  pg/ml for the diagnosis of HE was 98%.

No studies could determine a clear limiting value of BNP as regard HE as our study did, but studies done on heart failure and acute coronary syndrome showed that patients with BNP level of more than 80 pg/ml were significantly more likely to die, had a new or recurrent myocardial infarction, or had new or progressive heart failure than those with a level of 80 pg/ml or less as studies done by Dao et al. and James et al. [36,37]

## Conclusion

BNP can be used as a simple, rapid and easy test to perform and interpret as an early marker of heart or brain involvement during hypertensive crises and its evaluation should be very useful in patients admitted with acute and rapid elevation of BP.

## Limitations

We are aware of some limitations of our study. One of them is that a BNP determination at discharge time should be very useful to eventually clarify if increased level of BNP in HE is related or not to acute heart or brain injury or to the transient pathophysiological modification.

## Recommendations

We recommend continuing the study on a wide scale of patients to declare the use of BNP as a routine investigation in the ER or ICU to distinguish HE from HU and immediately identify patients who need further evaluation to limit target organ damage.

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