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The Validity of B-Type Natriuretic Peptide as a Rule-Out Test For Heart Failure in Patients With Acute Dyspnea Presented to the Emergency Room

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Original Article

Abstract

Background: *Dyspnea is a common symptom that can occur normally in healthy individuals subjected to heavy exertion, but is considered pathological otherwise. It may result from physiological, environmental, or psychological factors, but the primary causes are generally of respiratory or cardiac origin. B-type natriuretic peptide (BNP) is a principal cardiac hormone produced in large quantities by ventricular tissues, and elevated in cases of heart failure, acute coronary syndrome, valvular heart disease, atrial fibrillation, as well as due to reduced renal function.*

Aim of the Study: *To assess the validity of B-type natriuretic peptide as a rule-out test for heart failure in patients with acute dyspnea presented to the emergency room.*

Methodology: *This is a case-control study conducted in Al-Hussein Medical City Teaching Hospital from June through December 2019, and included patients presented to the emergency room with acute dyspnea. Patients were grouped into cases of heart failure and controls based on their echo-study findings, and clinical and laboratory data, including BNP level, were collected from them.*

Results: *The study included (57) patients divided into (29) cases and (28) controls. Mean age was (49.67 ± 14.85) years, with females forming about (60%) of study sample. BNP level was significantly higher among cases (778.17 ± 274.09) compared to controls (247.79 ± 86.52), P-value < 0.001. BNP was inversely correlated with ejection fraction (EF), correlation coefficient = -0.76, P-value < 0.001.*

Conclusions: *B-type natriuretic peptide (BNP) level is significantly higher among patients of heart failure in comparison to controls. The minimum cut-off value of BNP level for discriminating heart failure cases was (398.85) with a sensitivity of (90%) and specificity of (100%). BNP level was found to be inversely correlated with the ejection fraction (EF).*

Keywords: *Heart Failure, Dyspnea, Emergency, B-Type Natriuretic Peptide Test*

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1. INTRODUCTION

Dyspnea is a common and significant symptom that is defined as a "subjective experience of breathing discomfort that consists of qualitative distinct sensations that vary in intensity" [1]. It can occur normally in healthy individuals who are subjected to heavy exertion, but it is considered pathological otherwise and may result from various physiological, environmental, or psychological factors, but the primary causes of dyspnea are generally of respiratory origin or cardiac origin . The majority of cases of dyspnea are caused by asthma, myocardial ischemia, heart failure, chronic obstructive pulmonary disease (COPD), pneumonia, as well as trauma [2,3].

It is of significant importance to identify severe and life-threatening conditions of dyspnea, which can be clinically identified by certain red flag symptoms. These include hypotension, high respiratory rate, disturbed mental status, hypoxia, stridor, cyanosis, breathing effort without movement of air, signs of pneumothorax, and unstable arrhythma [2].

B-type natriuretic peptide (BNP) is a principal cardiac hormone that is produced in large quantities by the tissues of the ventricles of the heart [4]. BNP is one member of the natriuretic peptides (NP) family, which is a group of certain biological peptides that share similar structure, including the atrial natriuretic peptide (ANP), C-type natriuretic peptide (CNP), D-type natriuretic peptide (DNP), and urodilatin along with BNP [5].

It was first obtained in 1988 [6], and was discovered later that higher concentrations of BNP were present in the cardiac muscles [7]. The biologically active form of BNP is released from a pre-hormone named proBNP, which is formed of 108 amino acid sequence, that undergoes certain processes in order to release the biologically active BNP, composed of 32 amino acid sequence with a carboxyl group terminal [8,9].

BNP is expressed from the gene NPPB, which is composed of two introns and three exons, which expresses the pre-pro-BNP. Unlike ANP, which is readily stored in atrial granules and immediately released upon stimulation, BNP is transcribed on need as a response to certain cardiac stress conditions under the regulation of the nuclear transcription factor GATA-4[10].

BNP has a relatively short half-life of 20 minutes [11], and is present in blood in both the active from and inactive form [5]. Elimination of BNP is performed by specialized receptors that are present in certain organs of the body, such as in the liver, kidneys, lungs, and vascular

endothelium [12]. The normal value of BNP level in the human circulation are generally low, and is usually about 0.9 fmol/ml to 1.0 fmol/ml [7,13].

ProBNP has a longer half-life of 120 minutes, which is six times higher than that of BNP. This results in the presence of higher values of serum proBNP compared to the serum level of BNP, which may reach up to six times higher value, despite being released in molecularly equivalent proportions [9].

The main trigger for the release of BNP is the stretching of cardiac ventricle, which describe the elevation of BNP among patients with elevated left ventricular end diastolic pressure and patients with elevated pressure of the pulmonary artery [14]. Upon the presence of hypertrophic stimuli, the mRNA of BNP is quickly up-regulated alongside the up-regulation of BNP gene expression and secretion by the effect of pro-inflammatory cytokines (mainly interleukin 1-beta and tumor necrosis factor-alpha), therefore providing a high rate of BNP expression within the tissue[13].

Elevated BNP is observed clinically in cases of heart failure, acute coronary syndrome, valvular heart disease, atrial fibrillation, as well as in patients with reduced renal function [9], and may results in certain effects on the human body that are in favor of protecting the threatened heart which triggered the release of the hormone. These effects include vasodilation and natriuresis, as well as antifibrotic and metabolic effects [15].

These effects are achieved by certain mechanisms, such as inducing dilatation of the afferent renal arterioles and inducing constriction of the efferent ones; thereby increasing the glomerular filtration rate (GFR) and enhancing the diuresis and natriuresis [16].

Other mechanisms include reducing the cardiac preload and after-load, and the reduction of blood volume either by plasma sequestration (short-term) or by suppression of the renin-angiotensin-aldosterone system (RAAS) at certain levels (long-term) [17]. BNP also restricts the cardiac sympathetic nervous system responsiveness in order to further protect the endangered heart [18].

The receptor for BNP is natriuretic peptide receptor-A (NPR-A), which is the main receptor for both ANP and BNP. It has 5 N-linked sites of glycosylation and 3 disulfide bonds, and is present natively as either homo-dimer or homo-tetramer. The human gene for that receptor is composed of 21 introns and 22 exons and is located on the chromosome 1q21-22 [10].

Elevated levels of BNP in circulation generally demonstrate a cardiac compromise, particularly in relationship with the left ventricle end-diastolic wall tension, therefore it is used in clinical setting as a marker for conditions linked to dysfunction of the cardiac ventricles [19]. Although the concentration of BNP in the circulation of normal persons does not exceed 1 fmol/ml; people with congestive heart failure (CHF) may reach up to 300 fmol/ml [5].

The risk of mortality for patients with acute dyspnea is high, mostly due to dyspnea of cardiac causes such as acute heart failure [20]. Heart failure is described according to the European Society of Cardiology (ESC) as "a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress."[21].

Heart failure is classified according to the associated ejection fraction of the left ventricle (LVEF) into three main classes: heart failure with preserved ejection fraction (HFpEF), heart failure with mid-range ejection fraction (HFmrEF), and heart failure with reduced ejection fraction (HfrEF) [22].

Advanced heart failure was first described in 1998 as a clinical condition in which the left ventricular ejection fraction (LVEF) at rest is less than 30%, with a New York Heart Association (NYHA) class of III to IV, or a peak uptake of O2 of less than 14 ml/kg/min [23]. Later in 2004, the definition of advanced heart failure was described to be "a state in which patients have significant cardiac dysfunction with marked symptoms of dyspnea, fatigue, or symptoms relating to end-organ hypoperfusion at rest or with minimal exertion despite maximal medical therapy."[24].

In 2007, the Heart Failure Association (HFA), which are a part of the European Society of Cardiology (ESC), provided a new definition with outlined clinical characteristics [25]. These characteristics were further advanced into the 2013 guidelines for the management of heart failure by The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) [26]. Acute heart failure is considered a common cause for the hospitalization of people aged 65 years or more, with dyspnea being the main reason for hospitalization, which is usually accompanied by signs related to fluid overload, such as

pulmonary congestion or peripheral congestion [27].

Although dyspnea is considered as an important check point in the course of the clinical care provided to patients with acute heart failure, it is still difficult to measure dyspnea in objective manners, since it is a subjective symptom that is hard to measure or validate in a reliable manner [28]. Several mechanisms are responsible for dyspnea in acute heart failure, such as bronchoconstriction or pulmonary edema [29].

Congestion in acute heart failure is a key mechanism in the development of symptoms, which is caused by impaired regulation of sodium excretion by kidneys due to the activation of certain neuro-humoral pathways (mainly renin-angiotension-aldosterone system, arginine-vasopressin system) that are initialized in order to oppose the negative role of heart failure in the delivery of O2 to the tissues [30].

The diagnosis of acute heart failure is a challenging process, as the physical examination approach has a low sensitivity and specificity for its detection [31], therefore it is suggested that BNP may be utilized to detect cases of acute heart failure that are presented as acute dyspnea.

2. PATIENTS and METHODS

This study is a case-control study conducted in Al-Hussein Medical City Teaching Hospital and included patients presented to the emergency room with acute dyspnea as the most prominent symptom during the period from June 2019 through December 2019. Formal approvals were acquired before the initialization of data collection and clinical examination, as well as patient's verbal permission.

Inclusion Criteria:

• Patients of both sexes who were 18 years or older presented to the emergency room with complaint of dyspnea.

Exclusion Criteria:

Patient was excluded if he/she had one or more of the following:

1. Acute coronary syndrome
2. Primary/secondary pulmonary hypertension
3. Renal insufficiency
4. Sepsis
5. Pulmonary embolism
6. Chest trauma

Data collection:

Data for the study was collected by interviewing the patient before clinical examination, followed by detailed history taking and clinical examination. All patients underwent ECG using General Electric MAC 2000 device (GE Healthcare, United Kingdom). In addition, several laboratory investigations were performed including complete blood count, ESR, renal function test, D-dimer, BNP. C-reactive protein. Then patients who conform to the inclusion criteria of the study with no exclusion criteria were subjected to echo study by a specialist cardiologist in order to classify them into either cases with heart failure or controls without heart failure according to the ESC guidelines(21). Echo study was performed using CISPR-compliant echo device (Group I class A).

Statistical analysis:

SPSS® Software (version 23.0 for Linux®) was used to perform the statistical analysis for this study. Qualitative data are represented as numbers and percentages, while continuous numerical data are represented as mean ± standard deviation. P value of less than 0.05 was considered statistically significant.

3. RESULTS

This study included a total of (57) patients that attended the emergency room for acute dyspnea, (29) of them were cases with heart failure diagnosed by echo study (cases group), and the remaining (28) were patients who were confirmed to be free of heart failure by echo study (control group).

Age of participants ranged from (21) years to (80) years, with a mean age of (49.7 ± 14.9) years Females formed the majority of study participants (59.65%), while males formed the remaining (40.35%) of individuals included in the study. Majority of study participants were from urban residents (84.2%) while only (15.8%) from rural areas. However, both groups were almost matched for their demographic characteristics, (**Table 1**).

Comparison of BNP level between cases (heart failure) and controls was performed using Student's t-test. BNP level was found to be significantly higher among cases of heart failure (778.17 ± 274.09) compared to controls (247.79 ± 86.52), Student's t-test = 9.78, P-value < 0.001, (**Table 2**).

Receiver-Operating Characteristics (ROC) curve was utilized to estimate the cut-off value of

BNP level to distinguish between cases with heart failure and cases without heart failure. Minimum cut-off value of BNP level with excellent validity was (398.85) with (90%) sensitivity and (100%) specificity. Area under the curve (AUC) was (0.94) with 95% confidence interval of (0.88-1.00) and P-value < 0.001 (**Figure 1**).

Ejection fraction among cases ranged from (10%) to (65%) with a mean of (33.14% ± 13.56%), while among controls the ejection fraction ranged between (60%) to (73%) with a mean of (65.64% ± 2.95%). Pearson's product-moment correlation coefficient was calculated in order to assess the correlation between ejection fraction and BNP level. There was a statistically significant strong negative correlation between ejection fraction and BNP, with correlation coefficient (R) = -0.76, P-value < 0.001. The scatter plot diagram in (**Figure 2**) (5) illustrate the finding. Signs and symptoms were compared between cases and controls in (**Table 3**). Orthopnea was significantly higher among cases compared to controls, so as edema. However, cough was not significantly different between cases and controls.

Table 1. Age and gender distribution of the study participants

Variable	No.	%
Age (year)		
20 - 29	8	14
30 - 39	4	7
40 - 49	18	31.6
50 - 59	12	21.1
60 - 69	7	12.3
≥ 70	8	14
Mean (SD)	49.7 (14.9)	-
Range:	21-80	-
Gender		
Male	23	40.4
Female	34	59.6
Residence		
Urban	48	84.2
Rural	9	15.8
Total	57	100

Table 2. Comparison of BNP level with study group

Group	BNP Level		
	Mean	SD	Range
Case	778.17	274.09	127 - 1276
Control	247.79	86.52	107 - 395
Total	517.63	335.76	107 - 1276
P. value =0.001, Significant			

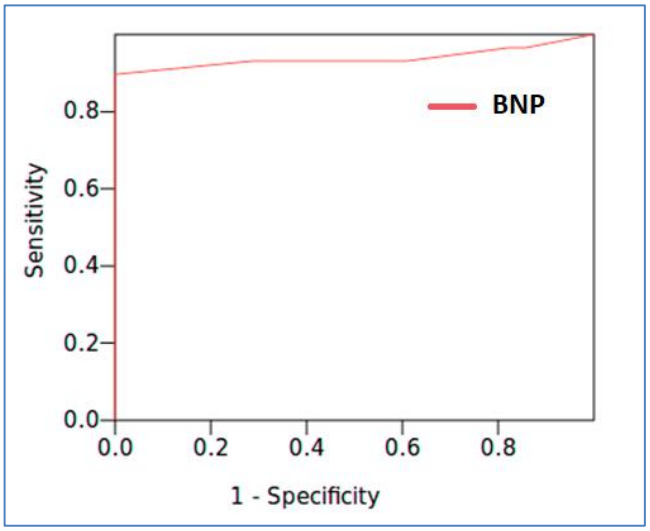

Figure 1. ROC curve for the performance of BNP in detection of heart failure in cases with acute dyspnea

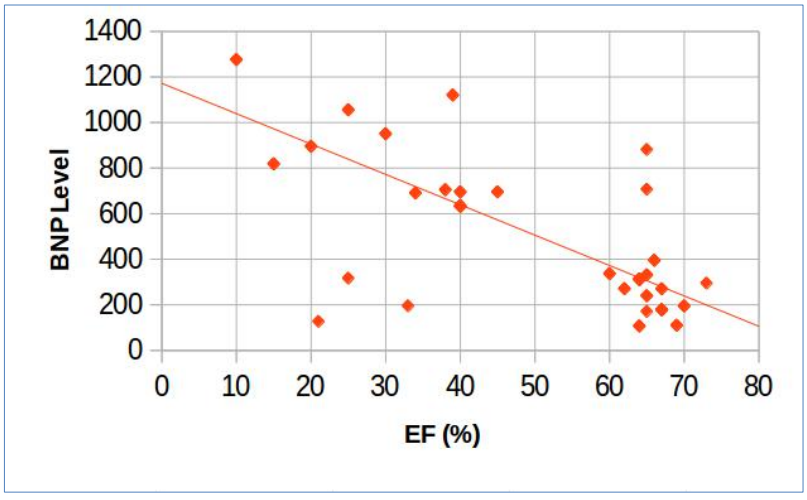

Figure 2. Scatter plot diagram showing correlation between BNP level (%)

Table 3. Signs and symptoms by study group

Signs and Symptoms		Case		Control		Total		P-value
		No.	%	No.	%	No.	%	
Cough	Yes	26	89.7	25	89.3	51	89.5	0.999F
	No	3	10.3	3	10.7	6	10.5	
Orthopnea	Yes	23	79.3	6	21.4	29	50.9	< 0.001*
	No	6	20.7	22	78.6	28	49.1	
Edema	Yes	22	75.9	0	0.0	22	38.6	< 0.001*F
	No	7	24.1	28	100.0	35	61.4	
* significant at P < 0.05, F: Calculated using Fisher exact test								

4. DISCUSSION

The present study had demonstrated that BNP level was significantly higher among patients with acute dyspnea due to heart failure when compared to patients with acute dyspnea due to other causes. This finding is supported by the finding by Al-Ibrahimi, Al-Gazally, and Alshok in their study conducted in Babylon – Iraq during the period from 2015 to 2016, and included a total of (70) patients, which demonstrated that BNP level was significantly higher among heart failure patients compared with controls [(32)]. However, the mean BNP level in the present study of (778) pg/ml is somewhat higher than that of Al-Ibrahimi et al. who reporte a mean of (681) pg/ml [(32)]. Another similar finding was presented by Maisel et al. in their prospective study which included 1586 patients admitted to the emergency department with acute dyspnea, with a mean BNP level of (675 ± 450) pg/ml [(33)]. Receiver-Operating Characteristics (ROC) analysis had revealed that a cut-off value of 399 ng/ml had a good sensitivity (90%) with an excellent specificity (100%). This means that, within the present study sample, patients with BNP of less than 399 ng/ml can be definitely ruled out from the presence of heart failure. A similar high validity of BNP for the prediction of heart failure was demonstrated by Al-Ibrahimi et al., with a sensitivity of (91.2%) and a specificity of (95.1%) [(32)]. The study by Maisel et al. had demonstrated a much lower cut-off value of 100 pg/ml, with a sensitivity of (90%) similar to the present study, but with a lower specificity of (76%) [(33)]. This variation could, in part, be attributed to the difference in the mean age of the patients of this study (64 years) compared to the mean age of patients in the present study (49.7 years). Another study by Villacorta et al. had suggested a cut-off value of 200 pg/ml, which was closer to the value demonstrated by the

present study, and had a higher validity (sensitivity of 100% and specificity of 97%)(34). The area under the curve in the present study was (0.94) with a 95% C.I. of (0.88 – 1.00), which was slightly higher than the finding of Maisel et al., which was 0.91 with 95% C.I. of (0.90 – 0.93) [33], but lower than that of Villacorta et al., who demonstrated an area under the curve of 0.99 [34]. In the present study, BNP level was found to be negatively correlated with ejection fraction, with correlation coefficient of -0.76 and P-value of < 0.001. This finding is consistent with the finding by Karakilic et al. who demonstrated a similar negative correlation with P-value of <0.01 [35]. Both orthopnea and edema were found to be significantly higher among cases with heart failure compared to patients with dyspnea due to other causes, with a P-value of <0.001. This finding is most likely explained by the well-known association of these symptoms with heart failure [36]. The study by Al-Nafii K, which was conducted in Karbala – Iraq in 2013 and 2014, and included a total of 425 patients, had demonstrated that NT-ProBNP measurement is valuable in patients with ventricular dysfunction who are presented with dyspnea [37]. It is worth noting that Omar and Guglin had suggested in their retrospective analysis in 2016 that a single BNP measurement at time of admission cannot reflect the severity of congestion, and proposed that other factors including age and BMI probably influence BNP value, affecting its utility as a predictor for the volume overload degree. However, the retrospective design of that study was considered its main limitation [38].

5. CONCLUSIONS

The present study concluded that B-type natriuretic peptide (BNP) level is significantly higher among patients of heart failure in comparison to controls. The minimum cut-off value of BNP level for discriminating heart failure cases was (398.85) with a sensitivity of (90%) and specificity of (100%). BNP level was found to be inversely correlated with the ejection fraction. We recommend,

Utilization of BNP level testing in patients complaining of acute dyspnea who are admitted to the emergency room, in order to predict the cases of dyspnea caused by heart failure. However, further studies that include larger sample size are recommended so as to be compared with the findings of the present study.

Ethical Clearance:

Ethical issues were taken from the research ethics committee. Informed consent was obtained from each participant. Data collection was in accordance with the World Medical Association (WMA) declaration of Helsinki for the Ethical Principles for Medical Research Involving Human Subjects, 2013 and all information and privacy of participants were kept confidentially.

Conflict of interest: Authors declared none

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