CLINICAL UTILITY OF PLASMA NT-PROBNP IN DIAGNOSING ACUTE DYSPNEA

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ABSTRACT

Objectives: To evaluate the clinical utility of NT-ProBNP assay in patients, admitted in Intensive care unit, with acute dyspnea.

Material & Methods: This Observational cross-sectional study was conducted at Combined Military Hospital Malir Cantt Karachi From Jan 2019 to Dec 2019. In this study, total 632 patients were selected with purposive non-probability sampling who were admitted in the intensive care unit (ICU) with acute dyspnea. ECGs, CXRs, Echo and plasma NT-ProBNP levels were analyzed along with other lab tests. Using the discharge diagnosis as the gold standard, clinical findings, provisional diagnoses and NT-ProBNP levels were cross tabulated with the final diagnosis. The Chi-square test for categorical data and student's t test for numerical data were applied and p value < 0.05 for significance level was applied to compare cardiac vs non-cardiac dyspnea. Further comparative analysis between the age groups was done by one-way ANOVA test.

Results: Of the total 632 cases studied of acute dyspnea, NT-proBNP levels were acutely raised in 73% of cases to a mean level of 19760pg/ml which were alarming numbers. These patients were categorized and treated as 'cardiac dyspnea with heart failure', as compared to the remaining 27% cases in which the NT-proBNP levels were either normal or marginally elevated with a mean value of 119 pg/ml. They were diagnosed and treated as 'non-cardiac dyspnea without heart failure' (p=0.001). The diagnostic accuracy of NT-proBNP at a cutoff of 400 pg/ml for age <45 years was 100% sensitivity but 34% specificity. An optimal strategy to identify acute Heart Failure (HF) was to use age-related cut-points, 800 pg/ml for ages >45 years having 98% sensitivity and 87% specificity.

Conclusions: NT-proBNP is a rapid and reliable cardiac biomarker which can revolutionize the clinician's approach towards diagnosing and treating the underlying cause of acute dyspnea. In addition, its serial essays can predict the prognosis and outcome of admitted patients.

Key Words: Dyspnea, Heart failure, Plasma NT-ProBNP.

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INTRODUCTION

Diagnosis of acute dyspnea in ICU settings can be challenging. An early diagnosis & management of these patients is of paramount importance as timely correct decisions can make critical difference in patient's outcome. In acute dyspnea due to heart failure, effective off-loading of fluid over-load, is the basic step in management, along with avoidance of I/V fluids. I/V fluids can lead to sudden deterioration with a possibly fatal outcome. Although a thorough clinical work-up can give a clue, but at times, when the patient is critical, neither a detailed history is available nor the clinical signs elicitable to suggest the possible underlying etiology. The Chest X-Ray (CXR) can be difficult to obtain as the patients are too ill to get these. Electrocardiogram (ECG) can at times be perfectly normal despite advanced heart damage [1]. The central cardiac pressures monitoring is not only an invasive procedure but its interpretation requires the operator's skills and advanced ICU set-ups. Echocardiography (echo) although is gold standard in evaluating the cardiac function and in differentiating between Heart failure with preserved ejection fraction (HFpEF) & heart failure with reduced ejection fraction (HFrEF), however, it is an expensive test and usually not available in all ICUs. In addition, specially trained physicians are required for proper Echo evaluation and expert operators. Similarly, it may be technically difficult as the patients are unable to lie flat due to orthopnea. The assays of NT-proBNP in such clinical scenarios can be of great help which are not only accurate, quick and easy to obtain & interpret but are also reliably specific and sensitive.

Brain Natriuretic Peptide (BNP) is actually a cardiac hormone secreted by the cardiac myocytes when the later are stretched in volume expansion or in pressure overload states as seen in heart failure or valvular heart disease. BNP is diuretic, natriuretic and vasodilatory in its action thus mitigating the pathological processes involved in the progression of

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heart failure. In cardiac myocytes BNP is secreted as a pre-pro-BNP molecule which is then cleaved into pro-BNP. Once it reaches the circulation, each molecule of pro-BNP is further cleaved into an inactive N Terminal pro-BNP (NT-proBNP) and an active part, BNP, which carries all its physiological effects on neuro-circulatory system. It is the inactive N terminal part which is detected in the assays and is a very reliable marker in differentiating acute dyspnea due to heart failure from non-cardiac dyspnea [2]. While BNP has a shorter half-life of approximately 20 min, NT-proBNP has a relatively longer half-life of approximately two hours. NT-proBNP is metabolized in kidneys, is about six folds more stable at 20^{o}C and is not significantly influenced by exercise and position of the patient as compared to the BNP [3].

As already pointed out, dyspnea due to HF is a common cause of ICU admissions & mortality especially in elderly patients [4]. NT-Pro BNP has proven to be a sensitive and specific biomarker in diagnosing heart failure [5]. The objective of this study was to determine the clinical utility of plasma NT-proBNP in differentiating the etiology of acute dyspnea in patients admitted in ICU.

MATERIAL AND METHODS

This observational cross-sectional study was conducted from Jan 2019 to Dec 2019 with purposive non-probability sampling technique. The study protocol was approved by the Ethical and Research Committee of the institute. A total of 632 consecutive patients who were admitted in ICU with severe dyspnea were included in the study after taking the informed consent. Diagnosed cases of pulmonary tuberculosis, pulmonary fibrosis and ischemic or dilated cardiomyopathy were excluded from the study in order to have a complete focus on those patients of severe dyspnea who were previously undiagnosed. Patients with a previous diagnosis of Chronic Obstructive Pulmonary Disease (COPD) were, however, not excluded from the study as it was felt that many patients were having a diagnostic label of COPD and quite many of those patients were having ‘cardiac dyspnea’ instead of underlying pulmonary pathology. Patients of chronic kidney disease were also excluded as the metabolism of NT-proBNP is affected in renal failure thus giving a falsely high value.

NT-proBNP analysis was performed by Electro Chemiluminescence Immunoassay (ECLIA) method on Cobas e-411 Auto-analyzer by Roche. Each patient’s data was recorded including demographics, detailed medical history, and investigations such as ECG, Echocardiography, chest X-ray, cardiac biomarkers, baseline hematology & biochemistry. Separate blood sample for NT-proBNP measurement were taken. Provisional diagnoses were compared with the final diagnoses at the time of discharge. Based on the discharge diagnosis, all patients were divided into two groups. Group ‘A’ comprised of all patients having acutely raised levels of NT-proBNP along with a history, clinical features or in-hospital work-up was suggestive of underlying cardiac disease as a possible cause of severe dyspnea. Group ‘B’ comprised of those in whom, neither the NT-proBNP levels were increased nor the convincing history, lab features or in-hospital work-up, suggestive of underlying cardiac pathology. Baseline characteristics were reported in counts and proportions or mean, minimum and maximum as appropriate. Comparisons of clinical characteristics between two groups were performed with chi-square tests for categorical data and Student's t-test for numerical data and one-way ANOVA test was applied for further analysis by dividing age groups into < 45 years, > 45 years with p-value of 0.05, level of significance. Sensitivity, specificity, positive predictive value and negative predictive value, and likelihood ratios, defined as the sum of the concordant cells divided by the sum of all cells in the two-by-two table, were computed. Positive likelihood ratios were defined as sensitivity / (100- specificity). Negative likelihood ratios were defined as (100-sensitivity) / specificity. All analyses were performed with statistical software (SPSS 23).

RESULTS

Six hundred thirty-two patients were enrolled over a period of 12 months with purposive non-probability sampling. Mean age was 61±16 years (range, 29-98 years). There was male predominance showing 356 males (57.33%) and 276 females (43.67%). After clinical assessment and final diagnosis, patients were divided into two groups. Group ‘A’ comprised of 460 patients (73%) having acutely raised levels of NT-proBNP along with a history, clinical features or in-hospital work-up suggestive of underlying cardiac disease as a possible cause of severe dyspnea. They were labelled as ‘cardiac patients. Group ‘B’ comprised of 172 patients (27%) in whom neither the NT-proBNP levels were increased nor convincing history, lab features or in-hospital work-up suggestive of underlying cardiac pathology. They were labelled as “non-cardiac patients”. The mean NT-proBNP levels in Group A were 19760 pg/ml (228-40000 pg/ml) compared with group B where the mean levels were

119pg/ml (20-1230 pg/ml) (p=0.001). NT-proBNP concentrations were higher in males (7866±1232) pg/ml compared to 6575±832 pg/ml in females (Tabel-1) in similar age groups. Increasing concentration of NT-proBNP was noted with increasing patients' age in group A, where NT-proBNP levels were 3071±1028 pg/ml, and 7238±8 p896g/ml pg/ml respectively in <45 & >45 years with (p=0.015). In younger patients (<45 years), an NT-ProBNP cut point of 400 pg/ml was 100% sensitive but only 34% specific, whereas in elderly patients (>45 years) the NT-ProBNP cut point of 800 pg/ml was 98% sensitive and 87% specific. The sensitivity of NT-proBNP among younger patients was thus outstanding but less specific as compared to older age group. As per manufacturer's claim high sensitivity (99%) and NPV (100%) age stratified cut points for <75 years are 125 pg/ml while the same are 450 pg/ml for those who are >75 years old, thus highlighting the significance of using the value for ruling out the diagnosis of HF in >45 years and using new cutoff for youngers ie <45 years in ICU setting.

Table-1: Clinical assessment and final diagnosis of dyspnea.

	Cardiac Dyspnea (n=460)	Non-Cardiac Dyspnea (n=172)	P-value
Age (years)	65-70	30-45	0.015
Male/ Female (%)	35/70	18/25	0.156
ECG (positive)	42%	9%	0.20
EF (mean)	46%	60%	0.100
cTnI (raised)	44%	5%	0.300
NT-ProBNP (pg/ml)	228-40000	20-1230	0.001

Table-2: Age stratified NT-proBNP cut points in heart failure

	Optimal value	Sensitivity (%)	Specificity (%)	Positive Predictive vale	Negative Predictive value	Likely hood ratio (+)	Likely hood ratio (-)
All patient	800	96	81	95	86	1.5	0.460
<45	400	100	34	82	98	5.1	0.200
>45	800	98	87	97	87	1.7	0.40

DISCUSSION

Diagnosing heart failure (HF) in patients presenting with acute dyspnea can be difficult because clinical assessment has a limited sensitivity and specificity [6]. Lainchbury *et al.* state that plasma NT-proBNP levels in patients with dyspnea due to CHF were significantly higher than those who have dyspnea due to non-cardiac condition [6]. NT-proBNP and BNP have a role in the diagnosis of heart failure and both have same diagnostic value. This was also identified by Mueller *et al* [7]. Higher sensitivity of NT-ProBNP and better correlation to the severity of HF than BNP was demonstrated by O'Donnoghlie *et al* [5]. The International Collaborative NT-proBNP study has defined appropriate cut-off levels through pooled data from many studies which suggest excellent diagnostic accuracy but broad range of cut-off levels exist in different baseline characteristics especially in different age groups [6]. NT-proBNP levels are inversely related to the ejection fraction (EF) of that patient measured by echocardiography. Lower EF has higher NT-proBNP levels, indicating poor heart functions. This was consistent with the findings of Lainchbury *et al* [6]. Our study proved that among the dyspneic patients with HF the plasma NT-proBNP levels were markedly raised as compared to those patients with non-cardiac dyspnea. This was also observed in study by Qin SU[1]. When the plasma NT-proBNP levels in age >45 years was above the reference value of 800 ng/L, the sensitivity, specificity, positive predictive value, and the negative predictive value were 98%, 87%, 97%, and 87%, respectively, same was also confirmed by Maisel AS[8]. It was found that NT-proBNP analysis is simple and quick and can be used in the differential diagnosis of cardiac and non-cardiac dyspnea and also as a prognostic marker of HF if tests are performed serially [9]. Use of NT-ProBNP as marker of prognosis in HF was demonstrated by Pascual Figal *et al* [9]. Their data suggested that serially decreasing NT-proBNP levels in a patient mark an improving patient's condition, whereas serially increasing NT-proBNP levels suggest deterioration of the patient's condition and poor outcomes. Our study, likewise proved that NT-proBNP levels were related to the clinical conditions of patients admitted into the ICU department. Serially monitored NT-proBNP levels revealed that NT-Pro BNP level in

CHF patients decreased significantly with the course of treatment reflecting an improvement of clinical condition [10]. This study also suggests that NT-proBNP is an easy to use test in diagnosing HF as compared to the echocardiography which has certain technical issues. Furthermore, recent studies prove that NT-proBNP can be used to identify individuals who have no heart dysfunctions but have increased risks of cardiovascular diseases and death [11]. Therefore, at present NT-proBNP is an important indicator in predicting patient outcomes.

Although NT-proBNP analysis provided high sensitivity and specificity for the diagnosis of HF but the level of NT-Pro BNP can be affected by certain factors like age, race, BMI, sepsis and renal function. Meta-analysis by *Porapakkham* suggested NT-ProBNP is not helpful as prognostic marker and does not reduce mortality in elderly >75 years of age due to multiple comorbidities [12]. NT-proBNP should be assessed along with patient's detailed history and clinical examination [13]. In addition, physicians should be aware of those other factors which may cause an increased level of NT-proBNP. When the NT-proBNP value is above the threshold, a possible HF should be considered. The NPV of NT-proBNP is more significant. When NT-proBNP is lower than 400 ng/L, the negative predictive value is 98%, providing a strong possibility of no HF. A rapid bedside testing of NT-proBNP can be used as a tool to facilitate differential diagnosis among patients with acute dyspnea, an excellent marker of prognosis and best predictor of HF patients. Consequently, the overall disease management and the treatment of these patients becomes more efficient and effective by the use of this specific test.

CONCLUSION

Plasma NT-proBNP is a rapid and reliable cardiac biomarker which can revolutionize the approach of treating physicians towards diagnosing and treating underlying cause of dyspnea. In addition, it is an excellent marker to predict the disease prognosis and outcome of patients, if performed serially, with dyspnea in ICU settings.

AUTHORS CONTRIBUTION

Shagufta Yousaf: Study design, introduction, material and methods & results.
Asif Nadeem: Discussion
Ghulam Murtaza: Statistics
Hamid Jamal Siddiqui: Conclusion, cases discussion
Muhammad Yasir Rafiq: Data references
Abeera Ahmad: Data collection,

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