

# Association of N-terminal-Pro-B-type Natriuretic Peptide with Localization of Thrombus and Clinical Outcome in Acute Pulmonary Embolism

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## ABSTRACT

**Introduction:** Pulmonary Embolism is a major health problem which is associated with significant mortality and morbidity. It is a common and lethal condition. This study was undertaken to find the association between NT-Pro-BNP levels and the localisation of thrombus in acute Pulmonary Embolism and to prognosticate the patients.

**Material and methods:** Prospective study conducted at a tertiary care hospital. Thirty patients with Pulmonary Embolism of various etiologies, confirmed with clinical features, laboratory investigations and imaging and fulfilling the inclusion and exclusion criteria were included. After getting informed consent, Blood samples for assessment of NT-Pro-BNP levels were collected within 24 hours of admission.

**Results:** In 19 patients, the thrombus was located centrally (in main pulmonary artery) whereas in 11 patients, the thrombus was located in the peripherally (in segmental and subsegmental pulmonary arteries). 22 participants of the study had normal clinical outcome. 5 patients were morbid (oxygen dependant/ heart failure) whereas 3 patients died. Patients with central pulmonary embolus had higher NT-Pro-BNP levels whereas patients with pulmonary embolus in the segmental or subsegmental pulmonary arteries had relatively less NT-Pro-BNP levels. Patients with high NT-Pro-BNP levels had complicated in-hospital course/ mortality whereas, patients with relatively lower NT-Pro-BNP had uncomplicated in-hospital course.

**Conclusion:** This study shows that higher NT-Pro-BNP levels indicate higher probability of a more central location of thrombus in pulmonary embolism and also right ventricular overload. Also patients with higher NT-Pro-BNP levels had a complicated in hospital course.

**Key words:** Pulmonary Embolism, Pulmonary Arteries, Right Heart Failure, NT Pro-BNP

thrombosis occurs in other sites. The incidence of PE in non-hospitalised patients is 3.5 per 10,000 person years while the incidence rate in hospitalised in-patients can be above 500 per 10,000 person years.<sup>1</sup> In India, VTE is a common cause of mortality and morbidity in patients hospitalized for medical or surgical illnesses. It is often misdiagnosed and not intervened in time. Though the exact magnitude of problem is not known in India, the clinical relevance and incidence is not expected to be different from Western countries. Acute PE has high early mortality rates. Despite the advances in diagnosis and treatment, the early mortality rates have not changed significantly. Due to the embolus obstructing the pulmonary bed, PE can result in a life threatening condition, acute right ventricular (RV) failure.<sup>2</sup> Early diagnosis is of paramount importance since most patients die within the first hours of presentation. Timely management is usually highly effective in reversing RV failure. The diagnosis of acute PE is based on the assessment of clinical likelihood, ECG, CXR, echocardiography, laboratory investigations, mainly D-dimer and cardiac biomarkers and imaging techniques (CT pulmonary angiogram). Several cardiac biomarkers have emerged as indicator of right ventricular dysfunction and clinical outcome predictor in patients with acute PE. Brain type natriuretic peptide (BNP) is a marker of ventricular dysfunction. Following cardiac myocyte stretch, this compound is released into the circulation. It is synthesized as an inactive pro hormone (Pro-BNP) which is split into active hormone BNP and an inactive N-terminal fragment (NT-Pro-BNP).<sup>3</sup> This study was undertaken to find the association between NT-Pro-BNP levels and the localisation

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## INTRODUCTION

Pulmonary Embolism (PE) is a major health problem which is associated with significant mortality and morbidity. It is a common and lethal condition. Pulmonary Thrombo Embolism (PTE) and deep vein thrombosis (DVT) collectively known as venous thromboembolism (VTE) encompass one disease entity. Among cardiovascular diseases, VTE along with stroke and myocardial infarction rank as three big cardiovascular killers. PTE implies partial or complete occlusion of pulmonary arterial circulation by the clot formed elsewhere usually in deep veins of the leg. Less than 5% of venous

of thrombus in acute PE, to monitor and prognosticate the patients closely.

Primary objectives of the study were to study the association of N-terminal-Pro-B-Type Natriuretic Peptide with localisation of thrombus in Acute Pulmonary Embolism and to study the association between NT-Pro-BNP levels and clinical outcome in patients with Acute Pulmonary Embolism and secondary objectives were to study on the various risk factors in patients diagnosed with acute pulmonary thrombo embolism and to follow up the patients at the end of 1 month to know the clinical outcome.

## MATERIAL AND METHODS

Prospective study was conducted at a tertiary care hospital, PSG Hospitals, Coimbatore. Thirty consecutive patients diagnosed to have pulmonary embolism were included in this study with the following criteria.

### Inclusion criteria

All patients of age more than 18 years with clinical and radiological evidence of acute PE will be included in the study.

#### 1) Clinical evidence

Patients presenting with dyspnoea, hemoptysis and chest pain with no acute ischemic changes in ECG and with normal Ejection fraction. ECG in acute pulmonary embolism will shows S1Q3T3 pattern.

#### 2) Radiological evidence

CT pulmonary angiogram showing filling defects within the pulmonary vasculature.

### Exclusion criteria

Patients with COPD, known case of Congestive cardiac failure and chronic kidney disease are excluded from this study.

After getting informed consent, Blood samples for assessment of NT-Pro-BNP levels were collected within 24 hours of admission. Risk factors for pulmonary

thrombo embolism were noted such as prolonged bed rest, hypertension, malignancy etc. Thrombi located in main/right/left pulmonary artery were classified as central while the others at segmental/sub-segmental levels were classified as peripheral. Echocardiographic findings such as ejection fraction, functions of right and left ventricle, pulmonary artery pressure were noted. Clinical course of the patient and clinical outcome were also noted. Clinical outcome of the patient at the end of one month was recorded by following up. Then descriptive and statistical analysis of location of thrombus and clinical outcome in relation with NT-Pro-BNP levels was done.

## STATISTICAL ANALYSIS

The data collected from the patients was tabulated using Microsoft excel. The data are reported as mean +/- SD depending on their distribution. Risk factors will be described in numbers and percentage. Any association will be analysed using chi-square test. Correlation will be analysed by Pearsman correlation. A p value of <0.05 using two tailed test was taken as being significant for all statistical tests. All data were analysed with statistical software package (SPSS version 24.0)

## RESULTS

In our study, we included 30 patients diagnosed with acute pulmonary thromboembolism. The mean age of study population is 57.6 years. 11 patients belonged to the group of 51 to 60 years. Only 2 patients were younger adults and 2 patients were old adults. Among the study group 17 patients were male (56.7%) and 13 patients were female (43.3%). In our study population following were the risk factors noted. Thirteen patients had prolonged immobilisation following road traffic accident or following major orthopaedic surgeries. 4 patients had underlying malignancy such as Ca lung or Ca breast. 13 patients had unprovoked PTE.(Table 1) The thrombus was located unilaterally in 19 patients whereas 11 patients have bilateral thrombus. In 19 patients, the thrombus was located centrally (that is, in main pulmonary artery) whereas in 11 patients, the thrombus is located in the peripherally (segmental and sub segmental pulmonary arteries).22 participants of the study had normal clinical outcome. 5 patients were morbid (oxygen dependant/ heart failure) whereas 3 patients died.(Table 2)

Patients with central pulmonary embolus have higher NT-Pro-BNP levels whereas patients with pulmonary embolus in the segmental or subsegmental pulmonary arteries have relatively less NT-Pro-BNP levels. And the difference between the two was statistically significant. (P= 0.02)(Table 3)

Patients with high NT-Pro-BNP levels had complicated in-hospital course/mortality whereas, patients with relatively

Risk factors	Frequency (n)	Percent (%)
Prolonged immobilization	13	43.3
Carcinoma	4	13.3
Unprovoked	13	43.3
Total	30	100.0

**Table-1:** Risk factors of the study participants

Clinical Outcome	Frequency (n)	Percent (%)
Normal	22	73.3
Morbid	5	16.7
Death	3	10.0
Total	30	100.0

**Table-2:** Clinical Outcome after 30 Days

	Localisation	N	Mean	Std. Deviation	P value
PROBNP	Central	19	6196.27	4377.75	.02*
	Peripheral	11	1529.10	2636.40	

**Table-3:** Association of PROBNP with localization

	Clinical Outcome	N	Mean	Std. Deviation	P value
PROBNP	Normal	22	3814.15	3860.52	.005*
	Morbid	5	3009.16	4033.77	
	Death	3	11864.00	1417.83	

**Table-4:** Association of PROBNP with Clinical Outcome

lower NT-Pro-BNP had uncomplicated in-hospital course. ( $P = 0.005$ )(Table 4)

## DISCUSSION

Acute PE shows wide variations in clinical presentation from asymptomatic course to a massive pulmonary embolism that may be fatal. When planning treatment for this condition, risk stratification is important. In this study 30 patients diagnosed with pulmonary embolism were included. The mean age of study population is 57.6 years. 17 patients were male (56.7%) and 13 patients were female (43.3%). The thrombus was located unilaterally in 19 patients whereas 11 patients had bilateral thrombus. In 19 patients, the thrombus was located centrally (main pulmonary artery) whereas in 11 patients the thrombus was located in the peripheral pulmonary artery (segmental and subsegmental pulmonary arteries). 22 participants of the study had normal clinical outcome. 5 patients were morbid (oxygen dependant/ heart failure) whereas 3 patients died. Patients with central pulmonary embolus have higher NT-Pro-BNP levels whereas patients with pulmonary embolus in the segmental or subsegmental pulmonary arteries have relatively less NT-Pro-BNP levels. And the difference between the two is statistically significant. ( $P = 0.02$ ).

Patients with high NT-Pro-BNP levels had complicated in-hospital course/ mortality whereas, patients with relatively lower NT-Pro-BNP had uncomplicated in hospital course. ( $P = 0.005$ ). From this study, it is evident that patients with higher NT-Pro-BNP levels have more central thrombus, have complicated in-hospital course and also cause morbidity and mortality. Whereas patients with comparatively lower NT-Pro-BNP levels have thrombus in segmental or subsegmental pulmonary arteries and they have an uncomplicated course. The findings of our study were consistent with many other similar studies.

In a prospective study conducted by Akpınar et.al in turkey in Forty-nine patients concluded that higher pro bnp levels indicate higher probability of a more central location of thrombus in pulmonary embolism, resulting a more adverse clinical course and also leading to right ventricular overload.. In a prospective study done by Pruszczyk et.al in Poland in 79 patients found NT-Pro-BNP to be a prognostic marker in acute pulmonary embolism.<sup>5</sup>

An Egyptian prospective study by A.Selem et al conducted in 64 patients concluded elevated NT pro-BNP in PE was associated with worse short term prognosis in terms of higher morbidity and mortality.<sup>6</sup> Another study, Heleder Dores et al a retrospective study also had similar results as that of our study which concluded that elevated NT pro-BNP in PE identified worse short term prognosis and also had excellent power to predict 30 day all cause mortality.<sup>7</sup>

In a meta analysis conducted by Frederikus et.al, in the Netherlands, they found that higher concentrations of NT-Pro-BNP distinguish patients with pulmonary embolism at higher risk of complicated in-hospital course and death from those with low NT-Pro-BNP levels.<sup>8</sup> In another meta analysis conducted by Cavallazzi et.al in USA, they found that NT-Pro-BNP levels are significant predictors of all cause in hospital or short term mortality.<sup>9</sup> A meta analysis by Guillaume Coutance et al concluded while elevated BNP levels can help to identify high risk of death and adverse outcome, the high negative predictive value of normal BNP levels is certainly more useful.<sup>10</sup>

From our study it is evident that NT-Pro-BNP levels are significant predictor of all cause in- hospital mortality in patients with acute PE. The potential outcome of our study is that patients with normal levels of NT-Pro-BNP have a high negative predictive value for unfavourable outcome. Patients with normal NT-Pro-BNP levels have low risk of death as well as for hemodynamic collapse. This was consistent with a study conducted by Nils Kucher in 73 patients which predicted that lower the pro-BNP levels, lower would be the hospital stay.<sup>11</sup>

Our study have a few limitations. First, the sample size is limited. Further studies including larger number of patients are necessary to clarify this point. Secondly, NT-pro-BNP is a precursor of BNP. The conversion of BNP to NT-Pro-BNP may take several minutes after myocardial stretch which may lead to false negative results in patients who present early. Serial monitoring of NT-Pro-BNP (eg. At admission and 6 hours later) may overcome this limitation.

## CONCLUSION

This study shows that higher NT-Pro-BNP levels indicate higher probability of a more central location of thrombus in pulmonary embolism and also leading to right ventricular overload. Also patients with higher NT-Pro-BNP levels had a complicated in-hospital course. Further studies with large number of patients were undertaken to determine the exact cut off levels of NT-Pro-BNP to help in treatment decisions.

## Ethical approval

The study was approved by the Institutional Ethics Committee

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