Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

A STUDY ON THE LEVEL OF SERUM NT PRO BNP IN VARIOUS CASES OF PRIMARY RESPIRATORY DISEASES PRESENTING TO EMERGENCY

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ABSTRACT

Introduction: PRO-BNP and NT PRO-BNP are such biomarkers which have been extensively studied for their role in differentiating the cause of dyspnea in a ER. As much as the troponins have been touted as the diagnostic milestone for ACS, the natriuretic peptides are being proposed for heart failure. Based on the robust data available the recent guidelines of ACS have incorporated PRO-BNP & NT PRO-BNP in their heart failure management protocol too.

Aims: To study the level of PRO-BNP in patients of various primary respiratory diseases presenting our emergency.

Materials and Methods: Patients of previously diagnosed/newly diagnosed with primary respiratory diseases mainly Pneumonitis, COPD, bronchial asthma, Bronchiectasis, ABPA, ILD who got admitted in Dr. Murari Lal Chest hospital of GSVM Medical College Kanpur were included in the study.

Result: In our study the mean PRO-BNP values progressively increases with hypoxemia with highest mean value 5257.66pg/ml in patients with severe hypoxemia of PaO2 <40mmhg followed by moderately hypoxic patients in range of 41mmhg-60mmhg having the mean value of 2052.47 pg/ml. Patients with arterial PaO2 in the range of 61.00mmhg – 80.00mmhg and >80.00mmhg have a modestly elevated PRO-BNP levels of PRO-BNP 336.02pg/ml and

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

252.5pg/ml. The mean PRO-BNP level progressively increased with the worsening hypoxemia and this difference was statistically significant ($p<0.0001$).

Conclusion: We found that the PRO-BNP marker at the time of admission in a respiratory emergency is a good prognostic marker for survival and should be done in all patients at the time of admission in respiratory emergency department.

Keywords: PRO-BNP, Respiratory emergency, COPD and Bronchiectasis.

INTRODUCTION

Diagnosis of diseases and assessment of severity of disease is the key to success in modern medicine. Clinical acumen of every physician is different and assessment of severity may vary from person to persons. To have an accurate diagnosis and assessment of severity of disease investigative work up is done.

Over the last 20 years technological advancement in investigation has taken a leap from basic hematological and radiological work up to the highest level of radiological, nuclear studies and assessment of biomarker as diagnostic as well as prognostic tool.

This era can be correctly described as an era of biomarkers. Numerous biomarkers have discovered, identified some even are repurposed for their diagnostic, prognostic values ,predicting severity and or probable complications well before their occurrence enabling us, the treating physicians to be in a better position to combat. The current pandemic of SARSCoV-2 is an excellent illustrator for this. As the saying goes necessity is the mother of invention, the need to identify the high risk patients in a respiratory illness and the necessity to avoid complications has forced us to find new biomarkers in this regard. Respiratory infection comprises the most important cause of critical illness and most common medical reason of mortality. The current pandemic of COVID-19 has shown us the strain faced by health care sectors all across the world and need to identify the patients who need most and certain intensive care in priority.

PRO-BNP and NT PRO-BNP are such biomarkers which have been extensively studied for their role in differentiating the cause of dyspnea in a ER. As much as the troponins have been touted as the diagnostic milestone for ACS, the natriuretic peptides are being proposed for heart failure.

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Based on the robust data available the recent guidelines of ACS have incorporated PRO-BNP & NT PRO-BNP in their heart failure management protocol too.

Though the cause for elevation of PRO-BNP IN respiratory disease is an interesting area of research, the severity of PRO BNP and NT PRO-BNP rise at the time of admission is the concern, because it may be a prognostic marker for the outcome of that respiratory illness

Hence they may be a good marker for triaging the patients with acute exacerbations of various respiratory illness even in patients without any evident of heart failure.

MATERIALS AND METHODS

Patients of previously diagnosed/newly diagnosed with primary respiratory diseases mainly Pneumonitis, COPD, bronchial asthma, Bronchiectasis, ABPA, ILD who got admitted in Dr. Murari Lal Chest hospital of GSVM Medical College Kanpur were included in the study.

Inclusion criteria:-

Patients being admitted in DR.MURARI LAL CHEST HOSPITAL with the primary diagnosis of various respiratory disease such as PNEUMONITIS,COPD,BRONCHAIL ASTHMA,BRONCHIECTASIS,ILD, PNEUMOTHORAX,HYDRO PNEUMOTHORAX AND PULMONAR EMBOLISM .

Exclusion criteria:-

1. Uncooperative patients.

2. Patients who were previously / subsequently diagnosed with left ventricular dysfunction by 2D echocardiography.

3. Patients having any structural cardiac disease/valvular heart disease/acute MI/grade 3and4 diastolic dysfunction.

4. Patients having systemic hypertension/pulmonary hypertension.

5. Patients having hepatic /renal /any other systemic illness .

6. Patients having immune compromised status.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

7. Patients not giving informed consent.

RESULT AND DISCUSSION

There were no studies on PRO-BNP levels significance in a pool of all respiratory illness. Most of the studies were done in a disease specific manner predominantly related to COPD and Pneumonitis.

When we look into the references in 2017 **suresh kumar** [1] et al conducted a similar study in India in patients of CAP where 34 patients were studied with 19 males and 15 females. This is almost similar to our study in terms of number. Another study by **Ebrahimzadeh**[2] et al in 2018 conducted a similar study in patients of copd with 96 males and 44 females which is similar to, sex ratio in our study population .

Overall 30 (60%) patients out of 50 had no comorbidities at presentation. Among the 20 patients with comorbidities, diabetes mellitus was predominant, presenting in 33.3% male patients and 11.7% females. Hypertension was also more in males than females (18% vs 11.7%).there were 3 patients presented with both diabetes and hypertension. Coronary artery disease was found in 2 males (6.1%) only. Hepatitis was found in 1 male patient. None of the female patient had either CAD or hepatitis. In **suresh kumar**[1] et al study about 19 patients did not have any complications (comorbidities) while 25 had complications (comorbidities) and most common complication (comorbidity) was diabetes mellitus followed by hypertension. This is very similar to our study population too. but in other large studies conducted outside India like the one conducted by **Adrish**[3] et al in 2017, 57 patients out of 167 in the study had comorbidities and the most common was hypertension followed by CAD.

19 (38%) of the presenting patients were smokers. out of 19 only 1 was female, which is expected in indian subset of patients similar to one conducted by **suresh kumar** [1] et al in 2017 which had about 28% of the study population predominantly males as smokers.

50 % of the patients had pneumonitis which were more or less equally distributed among males and females. This was followed by COPD being present in 30% of the patients. It was more in females (41.1%) than males (24.2%). There were 6% and 4% cases of Pneumothorax and Hydro

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

pneumothorax respectively, both in males. 8% patients presenting with exacerbations due to Interstitial lung disease which was slightly more common in males.

Among 33 males in the study the mean PRO-BNP value is 1442.4 pg/ml with a SD 1907.59. The mean PRO-BNP level among the 17 females was 1561.3pg/ml with an SD 2019.0. Overall the mean value of PRO-BNP among the study population was at 1430.0 pg/ml with an SD 1906.9. Thus the PRO-BNP value at the time of presentation was raised in every respiratory illness studied by us. These results are almost similar to many other studies, conducted on the similar diseases individually. In 2014 **Koichi nishimura**[4] et al 2014 from the Department Pulmonary Medicine, Kyoto University, Japan conducted a prospective trial in 61 patients with acute exacerbation of COPD and 191 patients with stable COPD. They measured the PRO-BNP levels at various intervals and found out that the level of median PRO-BNP in hospitalized patients were higher during exacerbation than before and after exacerbations [19.4pg/ml before exacerbation, 72.7pg/ml during exacerbation and 14.6 pg/ml after exacerbation. similarly, **Ebrahimzadeh**[2] et al in 2016-2017 conducted an cross sectional study involving about 140 patients of COPD exacerbations were taken and their PRO-BNP levels were measured. They found that the levels were indeed raised with a significant correlation between the mean serum level of PRO-BNP and the severity of acute exacerbation ($p=0.009$) some other smaller studies supporting this inference of ours in recent years include **EL GAZZAR**[5] et al [Egypt,2016] study which also found that the level of PRO-BNP was significantly higher in COPD patients [60.52 SD 30.99 pg/ml] than control [21.12 SD 4.62 pg/ml] and during remission [35.5 SD 16.54 pg/ml] ($p<0.05$) and in a 2016 Chinese study by **Cheng li**[6] et al about 61 patients with pneumonitis was included and their median PRO-BNP value was found to be about 2011 pg/ml with a range of 529pg/ml – 7216 pg/ml which far higher than the normal range

Another study similarly designed and conducted like our own study in Indian population was by **Suresh kumar**[1] et al in 2017 where in about 42 patients of community acquired pneumonia were studied for their PRO-BNP value. The mean PRO-BNP values were raised above the normal range at the time of admission like in our study.

There is marked difference in PRO-BNP value in exacerbations between patients who ultimately survived and those who could not survive. The mean PRO-BNP value of patients who survived was 519.93pg/ml while on the other hand the mean value of patients who could not survive was

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

4223.51pg/ml. This difference was found to be extremely significant statistically (p<0.0001) by oneway anova test. This finding of ours is supported by various other studies such as **Koichi Nishimura**[4] et al in 2014 also concluded from their study in Japanese COPD patients that the PRO-BNP levels was significantly higher in unsuccessfully discharged patients than successfully discharged ones [260.5pg/ml vs 48.5pg/ml] and in another 2014 study conducted by **Albina nowak**[7] et al with 341 patients of Community Acquired Pneumonia, their PRO-BNP levels were raised. This study also measured simultaneously the PRO-BNP and atrial natriuretic peptide to determine the significance of all the three peptides.

In a 2016 chinese study by **cheng li**[6] et al in 61 pneumonitis patients with Pneumonitis, the PRO-BNP levels of patients who survived was far higher at 3936pg/ml when compared to survivors at 1190 pg/ml even after excluding all the possibility for a cardiogenic cause .They also declared that the APACHE II and PRO-BNP values independently predicted the mortality of the patients. one among these studies which was conducted in India by **Suresh kumar**[1] at in 2017 found that the mean PRO-BNP value among those who died was 569.5 pg/ml and those who survived was 142.82 and this difference was significant (p=0.0001) which also corresponds to our study with the same level of significance.

Still robust evidence for this fact can be obtained from the systemic review and meta-analysis of six studies involving 967 patients done during this current ongoing covid-19 pandemic by **Rymond pranata**[8] et al PRO-BNP was higher in non-survivor group (standardised mean difference 0.75(0.44, 1.07), p<0.001; I2: 61%)than survivor group. Elevated PRO-BNP was associated with increased mortality (RR 3.63 (92.21, 5.95).

If we could take the severity of illness in terms of the outcome/mortality of illness then this implies that the PRO-BNP values at the time of presentation correlates very well with the severity of the exacerbation which brings us to one of the secondary endpoint taken in our study.

In our study the mean PRO-BNP values progressively increases with hypoxemia with highest mean value 5257.66pg/ml in patients with severe hypoxemia of PaO2 <40mmhg followed by moderately hypoxic patients in range of 41mmhg-60mmhg having the mean value of 2052.47 pg/ml. Patients with arterial PaO2 in the range of 61.00mmhg – 80.00mmhg and >80.00mmhg have a modestly elevated PRO-BNP levels of PRO-BNP 336.02pg/ml and 252.5pg/ml. The

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

mean PRO-BNP level progressively increased with the worsening hypoxemia and this difference was statistically significant ($p<0.0001$).

Many other studies have also proved this direct and strong relationship we have observed in our study between hypoxemia and PRO-BNP levels like in a slightly older 2011 study conducted in Japan by **cheng li**[6] et al in about 61 patients with acute exacerbations of COPD, found that the PRO-BNP levels correlated significantly with the PaO2 and paco2 levels.

This relation is actually even expected from physiology standpoint hypoxia in lung would naturally produce hypoxic vasoconstriction increasing the pulmonary vascular bed resistance.

Although many studies support this finding of ours few studies failed to prove this significance also mainly when **suresh kumar** [1]et al studied 41 patients of CAP in Indian population, the mean PRO-BNP values were raised above the normal range at the time of admission but they failed to show a significant difference between hypoxemia and PRO-BNP levels probably because they used spo2 as a surrogate in pace of PaO2 like in our study. Similarly in another prospective study done at Egypt in 2016 by of **EL GAZZAR**[5] et al at the Benham university by involving 50 patients with acute exacerbations COPD. They demonstrated a significant direct correlation with paco2 value and a non-significant negative correlation with pa02 value.

Our study values when plotted to obtain a Range of operator curve, the area under the curve was 0.708 which makes PRO-BNP a statistically significant prognostic marker for mortality. From the ROC plot, we can deduct that if we take the PRO-BNP value of 485.5 pg/ml we get a sensitivity and specificity of about 65% and 63% respectively for predicting mortality.

This finding is also supported by two other studies where they plotted ROC curve using their values .In **Albina nowak**[7] et al also concluded that PRO-BNP level as a independent predictor of mortality in their study . Their roc curve of all there peptides had comparable area (0.73) similar to our (0.70) implying the utility of PRO-BNP levels as a prognostic marker. **Rymond pranata**[8] et al conducted a systemic review and meta- analysis during the current 2020 COVID. A total of 967 patients from six studies were included in this analysis. Their analysis resulted in a sensitivity of 76% (46%–92%) and specificity of 88% (71%–96%). receiver operating characteristic curve analysis demonstrates an area under curve of 0.90 (0.87–0.93) signifying the importance.

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CONCLUSION

1. The mean PRO-BNP value of the study population consisting of exacerbations of PNEUMONITIS, COPD, PNEUMOTHORAX, HYDROPNEUMOTHORAX, PULMONARY EMBOLISM and INTERSTITIAL LUNG DISEASE was 1430.0pg/ml., 1442.3 pg/ml in males and 1561.30 pg/ml in females. The mean PRO-BNP values were raised in all the patients studied. Highest value was found in COPD followed by PNEUMONITIS. However, the levels were not significantly different between various diseases

2. The mean value of admitting PRO-BNP levels was 519.93 pg/ml in patients who were survived with treatment. he value was significantly high that is 4223.51 pg/ml in patients who didn't survive the treatment .

3. A progressive rise in PRO-BNP values correlating well with the level of hypoxemia with highest value in <40 mm/hg group (5257.65 pg/ml) and lowest value being in >80mm/hg group 252.3 pg/ml group ($p<0.0001$) .The PRO-BNP levels where however, did not correlate with the raising paco2 levels and ph levels.

4. We failed to be find significance correlation between PRO-BNP and PCO2, PH and Age as found in other studies.

5. Range of Operator curve (roc) plotting suggests that a PRO-BNP value of 473.0 to be the cutoff point for predicting mortality with a sensitivity of 65% and specificity of 63%.

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TABLE: DISTRIBUTION OF VARIOUS RESPIRATORY DISEASES AMONG STUDY POPULATION

MAIN DISEASE	MALE	FEMALE	TOTAL	PERCENTAGE
COPD	8 (24.2%)	7 (41.1%)	15	30%
PNEUMONITIS	17 (51.5%)	8(47.0%)	25	50%
PNEUMOTHORAX	3(9.0%)	0	3	6%
HYDROPNEUMO THORAX	2(6.0%)	0	2	4%
PULMONARY EMBOLISM	0	1(5.8%)	1	2%
INTERSTITIAL LUNG DISEASE	3(9.0%)	1(5.8%)	4	8%
TOTAL	33 (100%)	17 (100%)	50	100%

TABLE: CORRELATION WITH THE TLC COUNT

TLC COUNT	<4000	4000-12000	>12000
COPD	0	7	8
PNEUMONITIS	0	8	17
PNEUMOTHORAX	0	2	1
PULMONARY EMBOLISM	0	0	1
HYDRO	0	0	2

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

PNEUMOTHORAX			
ILD	0	3	1
TOTAL	0	20	30

TABLE: DIFFERENCE IN MEAN VALUES AMONG SURVIVORS AND NON SURVIVORS IN VAROUS DISEASE UNDER STUDY

DISEASE	MEAN Pro BNP Values					
	Survivors			Non-Survivors		
	No	Range	Mean Value	No	Range	Mean Value
PMEUMONITIS	19	40.3-1445.6	428.23	6	1606.0-5665.0	3779.17
COPD	11	9.0-1082.0	508.63	4	1128.0-6314.0	4157.5
ILD	3	389.0-984.0	692	1	-	5586
PNEUMOTHORAX	2	230.0-2716.0	1473	1	-	5584
HDROPNEUMOTHORAX	2	76.0-408.0	242	0	-	0
PULM EMBOLISM	0	-	0	1	-	4427.4
TOTAL	37		519.93	13		4223.51