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Study of NT-proBNP levels in Heart Failure and its Clinical Correlation - An Observational Study

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ABSTRACT:
Introduction: Heart Failure (HF) associated with significant morbidity and mortality. Normally, circulating levels of BNP and NT-proBNP are quite low, but the levels are increased in HF. This study aimed at: (1) To assess the role of NT-proBNP in diagnosis of HF. (2) To study the effect of various factors like age, BMI on NT-proBNP. (3) To find a relation between NT-proBNP levels and left ventricular ejection fraction (LVEF), disease severity and aetiology of HF.
Materials and methods: In this study, 100 patients of both genders having cardinal signs of HF were included. Blood samples were collected and used for estimation of NT-proBNP, urea, creatinine, RBS using autoanalyzer. Electrocardiogram, chest X-ray, and 2D Echo were obtained. 2D-Echo was used to confirm the diagnosis of HF and for estimation of LVEF.
Results: In this, 46 patients had IHD, 30 patients had DCM, 11 patients had COPD, 3 patients had anaemic HF, 3 patients had congenital heart disease etc. The median NT-proBNP levels for each age group was: < 40 years = 3550 pg/ml, 41 – 50 years = 4019 pg/ml, 51 – 60 years = 5700 pg/ml, 61-70 years = 11,200 pg/ml, 71 – 80 years = 9450 pg/ml and > 80 years = 18,890 pg/ml. Significant positive correlation was observed between NT-proBNP and age (r=0.601) (p= 0.041) and negative correlation was observed between LVEF and NT-proBNP (r= -0.560) (p= 0.004).
Conclusion: NT-proBNP levels may vary with factors like age, BMI and LVEF. NT-proBNP levels may help diagnosis of HF in addition to clinical findings.
Keywords:Heart Failure, left ventricular ejection fraction, NT-proBNP

1. Introduction

Heart Failure (HF) associatedwith significant morbidityand mortality(Lam CSP et al., 2018).Globally, more than26 million people are suffering from HF and cardiacdysfunction. Global burden of HF andcardiac dysfunction are increasing rapidly and substantially with aging of the population(Benjamin EJ et al., 2017;Savarese G and Lund LH, 2017).

In India**,** the prevalence of HF is in the range from 1.3 to 4.6 million**,** with an annual incidence of 0.4 to 1.8 million. Indian patients are younger than those in high-income countries. They also have a high in-hospital mortality than in high income countries (Human and Prabhakaran, 2010).Due to high morbidity and mortality, the diagnosis of HF and cardiac dysfunction is extremelyimportantCao Z.P et al., 2017; Chen JH et al., 20120).

Studies have reported the role of NT-pro-BNP in heart failure (Khibar Salah et al., 2019; James L. Januzzi et al., 2022).The precursor of natriuretic peptides (NPs)is pre-pro-BNP a 134 amino acid peptide, synthesized in myocytes and cleaved to prohormone with 108 amino acids (Rørth R et al., 2020).Pro-BNP is secreted in response to stretch and is quicklycleaved into 2 circulating fragments- the biologicallyactive 32-amino acid C-terminal BNP (B-type natriureticpeptide) and the inert 76-amino acid NT-proBNP (N-terminalpro-BNP) by circulating endopeptidases (Daniels LB and Maisel AS., 2007; Volpe M. 2014).N-terminal pro-BNP is functionally inert. Stimulation of NP receptor by BNP triggers natriuresis, diuresis, vasodilation, inhibition ofrenin, aldosterone, inhibition of fibrosis, regulating blood pressure (BP), blood volume and sodium balance (Cataliotti A et al.,2004; Diez, J. 2017).

Circulating levels of BNP and NT-proBNP levels are quite low, but the levels are raised in HF. Both fragments are widely used assignificant indicators for the clinical diagnosis of HF, cardiac dysfunction,predict outcomes, and tomonitor the effects of therapy (Jourdain P et al., 2007; Fonarow GC et al., 2008).

Aim and objectives:

1. To assess the role of NT-proBNP in the diagnosis of HF.
2. To study the effect of various factors like age, BMI on NT-proBNP.
3. To find a relation between NT-proBNP levels and left ventricular ejection fraction (LVEF), disease severity and aetiology of HF.

2. Material and Methods

This observational study was conducted in department of General Medicine, Akash Institute of Medical Sciences and Research Centre, Devanahalli, Bengaluru, Karnataka, India. In this study, 100 patients of both genders having cardinal signs of HF like pedal edema, basal crepitations, and neck vein distention were included as per the definition of HF given by ACCF/AHA 2013 (Yancy CW et al.,2013).

The patients with sepsis, acute respiratory distress syndrome, pulmonary embolism, lower respiratory tract infection, hyperthyroidism, liver cirrhosis and renal failure were excluded from the study. The study has been approved by Institutional Ethics Committee (IEC NO: AIMSRC/IEC/69/2023) and informed consent was obtained from study subjects.All the study subjects underwent detailed clinical examination. Demographic details were collected from all the subjects. Within 24 hours of onset of symptoms, venous blood samples were collected and centrifuged to obtain serum sample. The obtained serum sample was used for estimation of NT-prpBNP, serum urea, serum creatinine, random blood sugar using fully-autoanalyzer. Electrocardiogram, chest X-ray, and 2D Echo were obtained. CK-MB and Trop - Iwere sent when required. 2D-Echo was used to confirm the diagnosis of HF and for the estimation of LVEF. In this study, patients of HF were divided into 3 groups as per the ejection fraction according to the ESC guidelines(Ponikowski P et al., 2016).

Heart failure with reduced ejection fraction (HFrEF) EF ≤ 40%
Heart failure with mid-range ejection fraction (HFmEF) EF 41-49%
Heart failure with preserved ejection fraction (HFpEF) EF >50%
Assessment of NT- proBNP levels in patients presenting with acute onset dyspnea was done using the age-specific “cut-off” points set forth by American College of Cardiology guidelines (Table 1)(Yancy CW et al.,2013).

Age	NT-proBNP	Interpretation
	< 300 pg/ml	HF unlikely
< 50 years	> 450 pg/ml	HF likely
50-75 years	> 900 pg/ml	HF likely
> 75 years	> 1800 pg/ml	HF likely

Statistical analysis

Data was represented in numbers and percentages. Pearsons’s correlation was used to assess the correlation of NT-proBNP with age, BMI,and LVEF.P value < 0.05 considered as significant.

3. Results

In the present study, mean age of the study subjects was 56.1 years, the range being 25-86 years. About 75% of the study subjects were in the range of 41-70 years. Out of 100 subjects, 59 (59%) were males and 41 (41%) were females (Table2).

Table 2:Age and sex wise distribution of study subjects

Age (years)	Males	Females	Total	Percentage (%)
< 40	4	7	11	11
41-50	18	6	24	24
51-60	19	12	31	31
61-70	8	12	20	20
71-80	6	4	10	10
>80	4	0	4	4
Total	**59**	**41**	**100**	**100**

In this study, 46 patients had IHD, 30 patients had DCM, 11 patients had COPD, 3 patients had anaemic HF, 3patients had congenital heart disease, 2 had rheumatic heart disease (RHD), 2 had hypertensive HF. 3 patients had breathlessness due to unknown etiology.

In the current study, the median NT-proBNP levels for each age group was: < 40 years = 3550 pg/ml, 41 – 50 years = 4019 pg/ml, 51 – 60 years = 5700 pg/ml, 61-70 years = 11,200 pg/ml, 71 – 80 years = 9450 pg/ml and > 80 years = 18,890 pg/ml. It is observed that the NT-proBNP levels were increased with advancing age. Significant positive correlation was observed between NT-proBNP and age (r=0.601) (p= 0.041) as shown in table 3.

Table 3: NT-proBNP levels as per age - Min, Max and Median levels

Age (years)	No. of subjects	Min. NT-proBNP (pg/ml)	Max. NT-proBNP (pg/ml)	Median NT-proBNP (pg/ml)
< 40	11	100	11,506	3550
41-50	24	213	25,000	4019
51-60	31	501	25,000	5700
61-70	20	1321	25,000	11,200
71-80	10	5204	25,000	9450
> 80	4	11,206	25,000	18,890

The study subjects were categorized into underweight, healthy weight, overweight and obesity. However, NT-proBNP levels and BMI not showed any correlation.

The study subjects were divided into 3 groups according to LVEF (ESC guidelines). The median NT-proBNP levels for each group was HFpEF (LVEF ≥ 50%) = 1122 pg/ml, HFmEF (LVEF 40-49‰) = 6010 pg/ml, and HFrHF (LVEF < 40%) = 10,120 pg/ml. Significant negative correlation was observed between LVEF and NT-proBNP (r= -0.560) (p= 0.004) as shown in table 4.

Table 4: NT-proBNP levels as per LVEF - Min, Max and Median levels

LVEF	No. of subjects	Min. NT-proBNP (pg/ml)	Max. NT-proBNP (pg/ml)	Median NT-proBNP (pg/ml)
≤ 40%	71	189	25,000	9201
40-49%	10	706	25,000	6120
≥ 50%	19	41	11,203	1035

In this study, the diagnosis of HF was done by 2D Echo. The screening of NT-proBNP yielded a sensitivity of 96% and specificity of 60%. The positive predictive value and negative predictive value are 87% and 84% respectively (Table 5).

Table 5:Sensitivity and specificity of NT-proBNP

	HF as per 2D Echo		Total
	Yes	No	
Positive	76	10	86
Negative	2	12	14
Total	**78**	**22**	**100**

4. Discussion

In this study, 46 (46%) patients had IHD, 30 (30%) patients had DCM, 11 (11%) patients had COPD. These findings were similar to the findings of the Trivandrum Heart Registry, in which the most common cause of HF was IHD (72%), followed by DCM (13%) (Harikrishnan S. 2015).

In the present study, mean NT-proBNP levels were increased with advancing age and significant positive correlation was observed between NT-proBNP levels and age (r=0.601) (p= 0.041). This observation was supported by a study conducted by Jie Zhang et al., reported that NT-proBNP

increased with age, and was higher in female subjects <80 years old(Zhang J et al., 2019).Similarly, another study conducted by Amrane et al.,indicated a significant positive correlation between age and NT-proBNP levels(Amrane M et al., 2018).

The study subjects were divided into 3 groups according to LVEF. In this study, significant negative correlation was observed between LVEF and NT-proBNP (r= -0.560) (p= 0.004). Our findings were supported by Amulya C. Belagavi et al., reported that NT proBNP levels had a good correlation with worsening LVEF(Amulya C. Belagavi., 2012).Similarly, another study by Kabi et al. also reported inverse relation between NT-proBNP levels and EF(Kabi S.,2018).Also, other study by Bay et al., reported that the median NT-proBNP levels inversely correlated with LVEF (Bay M et al., 2013).Another study by Sarzani R,et al., study suggested that Testing for NT-proBNP should be strongly recommended in the hospitalized very elderly,because of very high prevalence of underlying HF and its impact on in-hospital mortality,to identify an underlying cardiac involvement (Sarzani R et al., 2019).

The diagnosis of HF was done by 2D Echo. The screening of NT-proBNP yielded a sensitivity of 96% and specificity of 60%. The positive predictive value and negative predictive value are 87% and 84% respectively.In a systematic review and meta-analysis by Tylor and Verbakel on the diagnostic accuracy of point-of-care NP reported a sensitivity of 0.99 (0.57-1.00) and specificity of 0.60 (0.44-0.74) at 135pg/ml for NT-proBNP (Tylor K et al., 2018).

The positive predictive value and negative predictive value are 87% and 84% respectively. This indicates NT-proBNP may be used to rule out HF. In a study conducted by Januzzi JL et al., reported the age-independent cut offof NT-proBNP< 300 pg/ml had a negative predictive value of 98% and positive predictive value of 71.7(Januzzi JL Jr et al., 2018).

5. Conclusion

The study results may conclude that the NT-proBNP levels were negatively correlated with LVEF. The levels were also significantly elevated with advancing age. NT-proBNP may help in or out HF in addition to clinical findings. Further studies with large sample size are recommended.

Conflict of Interest:

The authors declared that there is no conflict of interest.

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