A CLINICAL STUDY OF N-TERMINAL PRO-BNP LEVELS IN CONGESTIVE HEART FAILURELaxme Gowda¹, Basava Raju M. M²¹Associate Professor, Department of Medicine, Mysore Medical College and Research Institute, Mysore.²Associate Professor, Department of Medicine, Mysore Medical College and Research Institute, Mysore.**ABSTRACT****BACKGROUND**

Heart failure is one of the leading causes of morbidity and mortality in the Populations across the globe, as it is a common end point of many diseases viz. coronary artery diseases, cardiomyopathies, hypertension and many others enumerated in the forthcoming sections. So methodical management of this ailment will play a vital role in preventing unnecessary mortality and morbidity. Lot of research has been done in relation to better understanding of the pathophysiology of this disease as well as in the diagnostic and therapeutic techniques related to heart failure till date. Echocardiography in particular, has revolutionised the diagnosis of heart failure. In the forthcoming sections is on a very simple and quick method of diagnosis of heart failure viz. NT-pro BNP level estimation, which neither needs the echocardiography gadgets nor a skilled echotechnician/cardiologist to interpret the echocardiographic images. This might prove very handy, especially in situations where cardiologists and echocardiography are not accessible. Apart from diagnosis, it may as well be used for followup as well as for prognostication. So, efforts are towards making diagnosis of heart failure simpler.

MATERIALS AND METHODS

Patients admitted in Cardiology Ward, K R Hospital, attached to Mysore Medical College and Research Institute between January 2015 and August 2016 with reduced left ventricular ejection fraction on 2D echocardiography were selected as cases. Forty patients diagnosed with congestive cardiac failure were selected as the cases; 40 subjects with normal 2D echocardiography with normal renal function tests, normal Hb%, normal BMI were selected as controls.

RESULTS

The median value of NT pro-BNP was 2294 pg/mL in a total of 11 cases of acute heart failure. The median value was 3450 pg/mL in 29 patients with chronic heart failure. The median of acute and chronic heart failure cases taken together was 3193 pg/mL. Among the controls, the median value was < 20 pg/mL. Clearly, the cases had elevated blood levels of NT pro-BNP as compared to controls. Chronic cases had higher values of 60% of patients having breathlessness more for more than 1 year had NT pro-BNP values greater than 2000 pg/mL and majority of them had values > 10,000 pg/mL; 57% of patients with breathlessness of duration of 1 - 12 months had values > 2000 pg/mL and majority of them had values between 2000 - 10,000 pg/mL; 50% of the patients having breathlessness for 1 to 4 weeks had values between 1000 - 2000 pg/mL; 71% of patients with Grade 4 NYHA failure had NT pro-BNP values above 2000 pg/mL; 55% of patients with Grade 3 NYHA failure had NT pro-BNP values of 2000 pg/mL and 45% of Grade 3 NYHA failure had NT pro-BNP values between 100 - 2000 pg/mL; 50% each of patients with Grade 2 NYHA failure had values below and above 2000 pg/mL; 78% of the patients with LVEF < 30% had NT pro-BNP levels > 2000 pg/mL, 22% cases had values < 2000 pg/mL; 37% of patients with EF of 30% - 40% had > 2000 pg/mL, 63% of patients with LVEF 31% - 40% had NT pro-BNP levels < 2000 pg/mL. There were three cases of LVEF > 40% in the study and one had < 2000 pg/mL, while two others had > 2000 pg/mL.

CONCLUSION

This study emphasises the role of NT pro-BNP in the diagnosis of congestive heart failure. The level of NT pro-BNP rises exponentially with the onset of heart failure in contrast to BNP. So this creates a gross difference in blood values of NT pro-BNP in patients with congestive heart failure as compared to those without congestive failure. It also suggests its role in quantifying the degree of failure and duration of illness. So, NT pro-BNP is useful, both as a qualitative and quantitative test in congestive heart failure.

KEYWORDS

NT pro-BNP; Congestive Heart Failure; NYHA, LVEF.

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*Financial or Other, Competing Interest: None.**Submission 13-01-2017, Peer Review 28-01-2017,**Acceptance 01-02-2017, Published 13-02-2017.**Corresponding Author:**Dr. Laxme Gowda,**Associate Professor,**Mysore Medical College & Research Institute,**Mysore.**E-mail: laxmegowda@gmail.com**DOI: 10.14260/jemds/2017/214* **BACKGROUND**

Heart failure is one of the leading cause of morbidity and mortality in the populations across the globe, as it is a common end point of many diseases, viz. coronary artery diseases, cardiomyopathies, hypertension and many others enumerated in the forthcoming sections.^{1,2} So methodical management of this ailment will play a vital role in preventing unnecessary mortality and morbidity. Lot of research has been done in relation to better understanding of the pathophysiology of this disease as well as in the

diagnostic and therapeutic techniques related to heart failure till date. Echocardiography in particular has revolutionised the diagnosis of heart failure. In the forthcoming sections, we are focussing on a very simple and quick method of diagnosis of heart failure, viz. NT pro-BNP level estimation^{3,4} which neither needs the echocardiography gadgets nor a skilled echotechnician/cardiologist to interpret the echocardiographic images.^{5,6} This might prove very handy, especially in situations where cardiologists and echocardiography are not accessible. Apart from diagnosis, it may as well be used for followup as well as for prognostication.^{7,8} So, our efforts are towards making diagnosis of heart failure simpler.

Objectives

1. To look for levels of NT pro-BNP in patients with heart failure.
2. To look for correlation of the NT pro-BNP levels and the NYHA class of Heart Failure.
3. To look for the role of other variables such as age on the levels of NT pro-BNP in a patient with heart failure.

MATERIALS AND METHODS

Source of Data

After taking Ethical Committee Clearance and Informed Consent, patients were admitted in Cardiology Ward, KR Hospital, attached to Mysore Medical College and Research Institute between January 2015 and August 2016 with reduced left ventricular ejection fraction on 2D echocardiography were selected for the study.

Method of Collection of Data

Sample Size

40 patients diagnosed with congestive cardiac failure were selected as the cases; 40 subjects with normal 2D echocardiography with normal renal function tests, normal Hb%, normal BMI were selected as controls.

Sampling Method

Simple random sampling.

Inclusion Criteria

Patients admitted in KR Hospital diagnosed with clinical evidence of congestive heart failure with confirmation on 2D echocardiography.

Exclusion Criteria

1. Patients with abnormal renal function tests.
2. Obesity.
3. Anaemia.

Data were collected in a pre-tested proforma including detailed history, clinical examination and relevant investigations after consent.

Patients were subjected to the following Investigations -

1. Hb%.
2. Total count.
3. ESR.
4. Serum Urea.
5. Serum Creatinine.

6. Serum Electrolytes.
7. Liver function tests.
8. Fasting Lipid Profile.
9. Urine albumin, sugar and microscopy.
10. Electrocardiography.
11. Chest x-ray.
12. 2D echocardiography.
13. Serum NT pro-BNP.

RESULTS

A total of 40 cases of CHF were included in the study, out of which 11 were acute CHF and 29 were chronic CHF. Serum NT pro-BNP levels were measured for all of them. The median value of NT pro-BNP was 2294 pg/mL in a total of 11 cases of acute heart failure. The median value was 3450 pg/mL in 29 patients with chronic heart failure. The median of acute and chronic heart failure cases taken together was 3193 pg/mL. Among the controls, the median value was < 20 pg/mL. Clearly, the cases had elevated blood levels of NT pro-BNP as compared to controls. Chronic cases had higher values.

Category	Median Values of NT Pro-BNP (in pg/mL)
Acute heart failure	2294
Chronic heart failure	4422
Acute and chronic failure	3193
Controls	< 20

Table 1. Median Values of NT Pro-BNP

Risk Factors

Hypertension

Hypertension	Cases		Controls		Total	
	No.	%	No.	%	No.	%
Present	10	25	2	5	12	15
Absent	30	75	38	95	68	85
Total	40	100	40	100	80	100

Table 2. Hypertension in Cases and Controls

P = 2.

Risk factor in the form of hypertension was more among the cases (25%) than among the controls (5%).

Diabetes Mellitus

Diabetes Mellitus	Cases		Controls		Total	
	No.	%	No.	%	No.	%
Present	9	22.5	1	2.5	10	12.5
Absent	31	77.5	39	97.5	70	87.5
Total	40	100	40	100	80	100

Table 3. Diabetes Mellitus Type 2 in Cases and Controls

P = 0.007.

Diabetes mellitus type 2 was eight times more prevalent among the cases than among the controls.

	NT pro-BNP (pg/mL)				Total
	< 1000	1001-2000	2001-10,000	> 10,000	
Absent	0	0	1	0	1
Count %	0%	0%	100%	0%	100%
1 - 7 Days	1	0	1	0	2
Count %	50%	0%	50%	0%	100%
1 - 4 Weeks	0	4	3	1	8
Count %	0%	50%	37.5%	12.5%	100%
1 - 12 Months	5	4	8	4	21
Count %	23.8%	19%	38.1%	19%	100%
> 12 Months	1	1	2	3	7
Count %	14.3%	14.3%	28.6%	42.9%	100%
Total	7	9	15	8	39
Count %	17.9%	23.1%	38.5%	20.5%	100%

Table 4. Duration of Breathlessness versus NT Pro-BNP Levels

P = 0.561.

60% of patients having breathlessness for more than 1 year had NT pro-BNP values > 2000 pg/mL and majority of them had values > 10,000 pg/mL; 57% of patients with breathlessness of duration of 1 - 12 months had values > 2000 pg/mL and majority of them had values between 2000 - 10,000 pg/mL; 50% of the patients having breathlessness for 1 to 4 weeks had values between 1000 - 2000 pg/mL.

LVEF

LVEF	Cases		Controls		Total	
	No.	%	No.	%	No.	%
< 30	21	52.5	0	0	21	26.3
31 - 40	16	40	0	0	16	20
40+	3	7.5	40	100	43	53.7
Total	40	100	40	100	80	100

Table 5. LVEF in Cases and Controls

P = 0.000.

52.5% of the cases had left ventricular ejection fraction less than 30%.

40% of patients had EF between 31% and 40% and 7.5% patients had EF between 40% and 50%.

NT Pro-BNP Levels

NT Pro-BNP (pg/mL)	Cases		Controls		Total	
	No.	%	No.	%	No.	%
< 1000	7	17.5	40	100	47	58.8
1001 - 2000	10	25	0	0	10	12.5
20,001 - 10,000	15	37.5	0	0	15	18.7
> 10,000	8	20	0	0	8	10
Total	40	100	40	100	80	100

Table 6. NT Pro-BNP Levels in Cases and Control

P = 0.000.

37.5% of the cases had values of NT pro-BNP between 2000 and 10,000 pg/mL.

25% of cases had values between 1000 and 2000 pg/mL; 20% of cases had values > 10,000 pg/mL; 17.5% of cases had values < 1000 pg/mL and among them only one patient had value less than 100 pg/mL. All controls had values less than 100 pg/mL.

Serum NT pro-BNP Levels and the NYHA Grade of CHF

	NT pro-BNP (pg/mL)				Total
	< 1000	1001-2000	2001-10,000	> 10,000	
Grade 2 count	1	1	1	1	4
% of GRA.H	25.0%	25.0%	25.0%	25.0%	100.0%
Grade 3 count	6	7	11	5	29
% of GRA.H	20.7%	24.1%	37.9%	17.2%	100.0%
Grade 4 count	0	2	3	2	7
% of GRA.H	0%	28.6%	42.9%	28.6%	100.0%
Total count % of GRA.H	7	10	15	8	40
	17.5%	25.0%	37.5%	20.0%	100.0%

Table 7. Serum NT Pro-BNP Levels and the NYHA Grade of CHF

71% of patients with Grade 4 NYHA failure had NT pro-BNP values above 2000 pg/mL; 55% of patients with Grade 3 NYHA failure had NT pro-BNP values of 2000 pg/mL and 45% of Grade 3 NYHA failure had NT pro-BNP values between 100 and 2000 pg/mL; 50% each of patients with Grade 2 NYHA failure had values below and above 2000 pg/mL.

LVEF and Serum NT pro-BNP levels

	NT pro-BNP (pg/mL)				Total
	< 1000	1001-2000	2001-10,000	> 10,000	
LVEF < 30 count % of LVEF	1	5	10	5	21
	4.8%	23.8%	47.6%	23.8%	100.0%
31 - 40 count % of LVEF	5	5	4	2	16
	31.3%	31.3%	25.0%	12.5%	100.0%
40+ count % of LVEF	1	0	1	1	3
	33.3%	.0%	33.3%	33.3%	100.0%
Total count % of LVEF	7	10	15	8	40
	17.5%	25.0%	37.5%	20.0%	100.0%

Table 8. LVEF and Serum NT Pro-BNP Levels

78% of the patients with LVEF < 30% had NT pro-BNP levels > 2000 pg/mL, 22% cases had values < 2000 pg/mL; 37% of patients with EF of 30% - 40% had > 2000 pg/mL, 63% of patients with LVEF 31% - 40% had NT pro-BNP levels < 2000 pg/mL. There were three cases of LVEF > 40% in the study and one had < 2000 pg/mL, while two others had > 2000 pg/mL.

DISCUSSION

In present study the median concentration of NT pro-BNP were 2624, 3193 and < 20 pg/mL amongst the acute CHF, chronic CHF and controls. Januzzi et al^{8,9} study showed that for diagnosis of acute CHF cut-off of > 450 pg/mL and > 900 pg/mL for < 50 years and > 50 years group respectively were highly sensitive and specific. McDonough et al¹⁰ study had median NT pro-BNP values of 269.6 pg/mL congestive heart failure.

	NT pro-BNP Median values (pg/mL)	
	Present Study	McDonough et al Study
CHF	3193	269.6
Controls	< 20	20

Table 9. Median Serum NT Pro-BNP Levels

Yoshihiko et al⁷ showed that blood level of NT pro-BNP rises exponentially with clinical grade of heart failure: Levels in Class II NYHA CHF were 25 times more than in class I NYHA. Levels in Class III NYHA CHF cases were 100 times more than in Class I NYHA.

In the present study 29 cases were Grade III NYHA, 7 cases were Grade IV NYHA and 4 were Grade II NYHA CHF. The higher median value in the present study thus could be because most of the cases were Grade III or IV NYHA congestive heart failures.

Among cases 11 cases were acute heart failure and their median value was 2294 pg/mL. Among the 29 chronic heart failure cases, the median was 4422 pg/mL.

Thus, chronic cases had more median value than the acute cases. There were 7 cases who had values less than 1000 pg/mL, out of which one was acute and others were chronic. This probably could be explained because many of the chronic cases were already begun on treatment by the time they were referred to the tertiary centre at KR Hospital. Studies have shown that the values start dropping significantly if heart failure is optimally treated.^{11,12}

In this study, we had higher values of NT pro-BNP in patients of age above 60 years as compared to those below 60 years: 56% of patients below 60 years had values above 2000 pg/mL, whereas 73% of patients aged above 60 years had values above 2000 pg/mL.

Bay et al¹³ showed higher values of NT pro-BNP in elderly patients. The cause of which was attributed to poorer GFR in elderly patients. Thus, this justifies that age could behave as a confounding factor provided a different cut-off was taken for elderly and others.

	Present Study (n = 40)	Yoshihiko et al (n = 390)	Bay et al (n = 2193)
Mean NT pro-BNP values in > 60 years as Compared to < 60 years	Higher	Higher	Higher

Table 10. Mean Serum NT Pro-BNP in People > 60 Years and < 60 Years

This study had fairly equal proportion of male and female cases. There was no significant difference in the NT pro-BNP values among males and females for a given NYHA class heart failure and for a given LVEF. Studies done by Yoshihiko et al showed significant higher values in females for a given class of heart failure.

	Present Study (n=40)	Yoshihiko et al (n=390)	Bay et al (n=2193)
Values of NT pro-BNP in Females as compared to Males	No Difference	Females > Males	Females > Males

Table 11. Mean Serum NT Pro-BNP Values in Females versus Males

Present study shows correlation between levels of NT pro-BNP and the duration of exertional breathlessness, which is a cardinal symptom of congestive heart failure. Exertional breathlessness was a presenting complaint in 39 out of the 40 cases in the present study; 60% of patients having breathlessness for more than 1 year had NT pro-BNP values

greater than 2000 pg/mL and majority of them had values > 10,000 pg/mL; 57% of patients with breathlessness of duration of 1 - 12 months had values > 2000 pg/mL and majority of them had values between 2000 and 10,000 pg/mL; 50% of the patients having breathlessness for 1 to 4 weeks had values between 1000 and 2000 pg/mL.

This prompts at a prospect of using this marker to not only classify severity of heart failure, but also as a marker of duration of heart failure. As of now, no studies have compared levels of NT pro-BNP levels in acute and chronic heart failure cases. In the present study, most of the cases were ischaemic congestive heart failure. So the correlation of NT pro-BNP levels to the aetiology of CHF could not be commented upon. In Copernicus sub-study,¹⁴ it was shown that the levels of NT pro-BNP were higher in patients with ischaemic CHF as compared to those with non-ischaemic CHF.

In the present study, there was a correlation of the NYHA grade of the heart failure to the levels of NT pro-BNP.

	Grade II NYHA CHF	Grade III NYHA CHF	Grade IV NYHA CHF
Median NT pro-BNP Levels in Present Study	2491	2953	7329
Mean NT pro-BNP Levels in Study at Iowa	1666	3029	3465

Table 12. Serum NT Pro-BNP Values in various NYHA Grade of CHF

In the present study, there is a correlation between the LVEF and the NT pro-BNP levels in the plasma; 71% patients having LVEF of < 30% had NT pro-BNP levels above 2000 pg/mL, 63% of patients with LVEF of 31% - 40% had NT pro-BNP levels between 1000 and 2000 pg/mL. These results are in tune with PRIDE study⁹ and Yoshihiko et al⁷ study.

	Present Study (n=40)	Pride Study (n=209)	Yoshihiko et al (n=390)
Correlation between LVEF and NT pro-BNP Levels	Present	Present	Present

Table 13. LVEF and Serum NT Pro-BNP Levels

CONCLUSION

Present study emphasises on the role of NT pro-BNP in the diagnosis of congestive heart failure. The level of NT pro-BNP rises exponentially with the onset of heart failure in contrast to BNP. So this creates a gross difference in blood values of NT pro-BNP in patients with congestive heart failure as compared to those without congestive failure.

It also suggests its role in quantifying the degree of failure and duration of illness. So NT pro-BNP is useful both as a qualitative and quantitative test in congestive heart failure.

Summary

This a case control study of levels of NT pro-BNP among 40 cases of CHF patients admitted in K R Hospital during the period of January 2015 to August 2016 who were randomly selected and NT pro-BNP measured along with recording other historical and investigational variables. Cases were compared with matched controls.

There was a median value of 3193 pg/mL among the cases, 2624 pg/mL among acute cases and 3450 pg/mL among chronic cases, whereas median in controls were < 20

pg/mL. NT pro-BNP values were higher among patients above 60 years as compared to patients younger to them.

Patients with longer duration of exertional breathlessness had higher values as compared to those with lesser duration of breathlessness, i.e. patients with chronic heart failure had values higher than those with acute heart failure. Higher values of NT pro-BNP were found among patients with higher clinical grade of heart failure and patients with lesser ejection fraction had higher median value of NT pro-BNP. Sex had no bearing on the levels of NT pro-BNP in this study.

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