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**Original Research Article**

# N TERMINAL-PRO BRAIN NATRIURETIC PEPTIDE (NT PRO BNP) LEVELS IN CONGESTIVE CARDIAC FAILURE

**Dr Shriram Agrawal[1], Dr Vijay Garg[2] (Professor) & Dr R. G. Dhawale[3] (Professor)**

CONSULTANT CARDIOLOGIST, AGRAWAL NURSING HOME, NARMADAPURAM, M.P.[1]
MD, FIAE, FICP,FCSI,FICA(USA),FISE,FACC(USA) ,FIMSA ,FISC, FESC(EUROPE), DEPARTMENT OF GENERAL MEDICINE, R.D. GARDI MEDICAL COLLEGE, UJJAIN, M.P.[2]
MSc, M.D. (GENERAL MEDICINE), R.D. GARDI MEDICAL COLLEGE, UJJAIN, MP[3]

**CORRESPONDING AUTHOR**: DR. SHRIRAM AGRAWAL
[MD (Medicine), DNB (Medicine), DM (Cardiology), DrNB (Cardiology)]
shriramagrawal@yahoo.com

**ABSTRACT**

**Background**- HF according to recent definition is described as a clinical illness characterized by signs and/or symptoms brought on by a structural or functional cardiac defect, which was supported by objective evidence of systemic or pulmonary congestion or by high levels of natriuretic peptide. We aimed to assess the role of N Terminal-Pro Brain Natriuretic Peptide (Nt Pro BNP) levels in Congestive Cardiac Failure and controls as well as to assess its correlation with age, gender, body mass index, troponin, electrocardiographic and 2D echocardiographic abnormalities in patients with CCF.

**Methodology**- This study was conducted as a case control study on patients with Congestive Cardiac Failure according to Framingham criteria presenting at tertiary care hospital during the study period of 18 months i.e. 01/06/2022 to 30/11/2023 in central India. A total of 100 cases with HF and 30 controls were included and were subjected to detailed history, clinical examination and routine and special investigations like NT pro BNP.

**Results**- NT Pro BNP was found to be raised (>400 ng/ml) in 96% cases and 10% controls and the observed difference was statistically significant ($p<0.05$). Our study found no significant association of NT ProBNP with age, gender, BMI as well as Troponin I ($p>0.5$), however, ECG as well as echocardiographic abnormalities correlated with NT Pro BNP significantly ($p<0.05$).

**Conclusion**- NT-Pro BNP is a valuable marker for diagnosis of congestive heart failure and its values correlate well with ECG and Echocardiographic abnormalities. The seriousness, gravity of congestive cardiac failure and higher NT Pro BNP levels warned the urgent need of critical care. Hence NT Pro BNP levels in patients of congestive cardiac failure had a prognostic value too.

**Keywords**- NT-Pro BNP, Heart failure, Echocardiography, Electrocardiogram, Framingham criteria, Ejection Fraction, Congestive Cardiac Failure.

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## 1. INTRODUCTION

Heart failure (HF) is a common complex cardiovascular condition resulting from structural or functional impairment of the ventricles attributing to significant dysfunction of left ventricles.[1]The diminished capacity of the heart to pump and/or fill with blood, or an anomaly in the structure or function of the heart resulting in either an insufficient cardiac output or adequate cardiac output as a result of compensatory neurohormonal activation and elevated left ventricular filling pressure, are the hallmarks of heart failure. Major international scientific organizations suggested a consensus on a common description and categorization of HF in 2021. HF was described as a clinical illness characterized by signs and/or symptoms brought on by a structural or functional cardiac defect, which was supported by objective evidence of systemic or pulmonary congestion or by high levels of natriuretic peptide. HF was categorized into three EF groups based on left ventricular ejection fraction (EF): HF with reduced EF (HFrEF), mildly reduced EF (HFmrEF), (mid-range ejection fraction), and preserved EF (HFpEF), with EF ranges of ≤40%, 41–49%, and ≥50%, respectively. Furthermore, a new entity, known as HF with improved EF, was developed and described as HF with a baseline EF of < 40%, a ≥ 10-point rise in EF from the baseline, and a second measurement of EF > 40% based on the trajectory of EF over time.[2]

Heart Failure is a burgeoning problem worldwide and has been described as a global pandemic with approximately 64.3 million people suffering from heart failure across the globe.[3] The prevalence of HF in India is estimated to be approximately 1% with incidence varying between 0.5 and 1.7 cases per 1000 person years.[4] The burden of heart failure is reported to increase with age and is documented to be higher among males as compared to females. The overall prevalence of HF is postulated to increase globally due to increase in burden of risk factors associated with heart failure such as diabetes, obesity, inadequate physical activity and unhealthy diet as well as increase in life expectancy and longer survival after treatment of underlying cardiac complications such as myocardial infarction (MI), valvular heart disease, and arrhythmias.[5]

Unlike western countries where heart failure is predominantly a disease of the elderly, in India it affects younger age group. Important risk factors include coronary artery disease, hypertension, diabetes mellitus, valvular heart disease, cardiomyopathies, obesity and cardiotoxic drugs. Rheumatic heart disease is still a common cause of heart failure in Indians.[6] For the diagnosis of HF a variety of diagnostic tests are available including assessment of clinical signs and symptoms of HF, laboratory blood tests, radiological examinations, electrocardiography and echocardiography. The definitive diagnosis of heart failure by clinical means is sometimes questionable, when associated chronic pulmonary and cardiac diseases are present.[7]

In 1998, a new cardiac natriuretic peptide, B type Natriuretic Peptide (BNP) was discovered. Three types of natriuretic peptides have currently been identified in human serum: atrial type (ANP), brain type (BNP) and C type (CNP). BNP and ANP are hormones, which are initially synthesized as pro-hormones and later cleaved into their active hormone states, in part due to response to ventricular wall stretch as seen in congestive heart disease. In this process, the

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active hormone is created (BNP) along with an inactive N-terminal fraction (NT ProBNP) in a 1 to 1 ratio. While both BNP and NT ProBNP are used diagnostically, the serum concentrations of NT-proBNP are considerably higher than BNP due to its longer half-life and greater stability.[8] Consequently NT-proBNP has provided better utilization as a marker for CVD , which in the following years was shown to have prognostic properties and later also appeared to have diagnostic properties in the emergency department and outpatient settings.[9-11] Cardiologists, primary care physicians, and other clinicians became enthusiastic about the role of natriuretic peptides in diagnosis of HF patients and thus, we aimed to assess the role of N Terminal-Pro Brain Natriuretic Peptide (Nt Pro BNP) levels in Congestive Cardiac Failure and controls as well as to assess its correlation with age, gender, body mass index, troponin, electrocardiographic and 2D echocardiographic abnormalities in patients with CCF.

## 2. METHODOLOGY

This study was conducted as a case control study on patients with Congestive Cardiac Failure presenting at Department of Medicine, R. D. Gardi Medical College and C.R.G. Hospital, Ujjain, M.P, during the study period of 18 months i.e. from 01/06/2022 to 30/11/2023. All patients admitted in CRG Hospital, diagnosed as congestive cardiac failure as per Framingham Criteria in the age group of 30-90 years and willing to give written consent for participation were included in the study.

Framingham Criteria for Congestive Heart Failure Diagnosis of CHF requires the simultaneous presence of at least 2 major criteria OR 1 major criterion in conjunction with 2 minor criteria.

| **Major criteria** | **Minor criteria** |
|---|---|
| • Paroxysmal nocturnal dyspnoea<br>• Neck vein distension<br>• Rales<br>•Radiographic cardiomegaly (increasing heart size on chest radiography)<br>• Acute pulmonary edema<br>• S3 gallop<br>•Increased central venous pressure (>16cm H2o at right atrium)<br>• Hepatojugular reflux<br>• Weight loss >4.5 kg in 5 days in response to treatment | • Bilateral ankle edema.<br>• Nocturnal cough.<br>•Dyspnea on ordinary exertion.<br>• Hepatomegaly.<br>• Pleural effusion.<br>• Decrease in vital capacity by one third from maximum recorded.<br>• Tachycardia (heart rate>100 beats/min). |

However, patients with Lung cancer, pulmonary embolism, ARDS, cirrhosis, renal failure, and septicemia were excluded from the study.

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After obtaining ethical clearance from Institute's ethical committee, a total of 146 cases of CCF admitted in ICU/ICCU were selected and were explained about the study and were asked to give written consent. Of them, 28 cases were excluded as they did not fulfil the inclusion criteria or were not willing to participate in study. Thus, a total of 118 cases were selected and were subjected for detailed history, clinical examination and routine and special investigations like NT pro BNP. Further out of these one hundred eighteen cases, eighteen did not cooperate for the complete investigations and left their participation. Hence one hundred cases formed the material of the present study and included in group A and age and sex matched thirty (30) healthy individuals included in control group.

**VITROS Immunodiagnostic Products NT-pro BNP Reagent Pack**: The quantitative measurement of N- terminal pro Brain Natriuretic Peptide (NT-pro BNP) in human serum and plasma (EDTA or heparin) was done using the VITROS ECi/ECiQ Immunodiagnostic Systems, the VITROS 3600 Immunodiagnostic System and the VITROS 5600 Integrated System to aid in the diagnosis of congestive heart failure and for the risk stratification of acute coronary syndrome and congestive heart failure.

**Principles of the procedure:** The VITROS NT-pro BNP test was performed using the VITROS NT-pro BNP Reagent Pack and the VITROS NT-pro BNP Calibrators on the VITROS ECi/EciQ Immunodiagnostic Systems, the VITROS 3600 Immunodiagnostic System and the VITROS 5600 Integrated System using Intellicheck Technology. An immunometric immunoassay technique is used, which and a horseradish peroxidase (HRP) – labelled antibody conjugate (sheep anti – NT –proBNP) The antigen - antibody complex was captured by streptavidin on the wells. Unbound materials were removed by washing. The bound HRP conjugate was measured by a luminescent reaction. A reagent containing luminogenic substrates (a luminal derivative and a peracid salt) and an electron transfer agent was added to the wells. The HRP in the bound conjugate catalyses the oxidation of the luminal derivative, producing light. The electron transfer agent (a substituted acetanilide) increases the level of light produced and prolongs its emission. The light signals are read by the system. The amount of HRP conjugate bound is directly proportional to the concentration of NT-pro BNP present.

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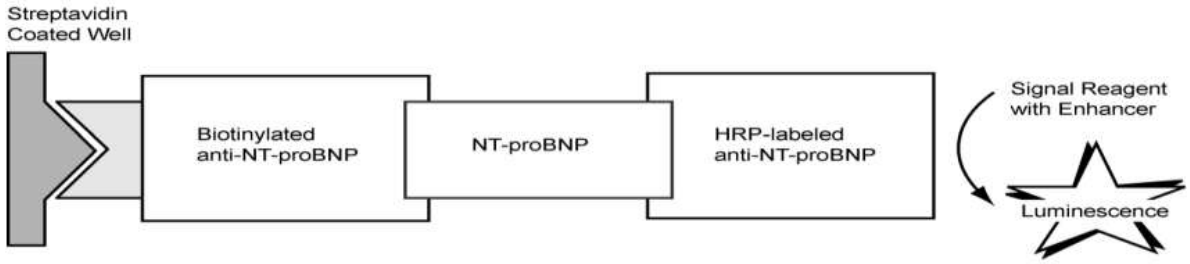
| Test Type | System | Incubation Time | Time to first result | Test Temperature | Reaction Sampl Volume |
|---|---|---|---|---|---|
| Immunometric | ECi/ECiQ, 3600, 5600 | 8 minutes | 16 minutes | 37 C | 40 µL |




**Statistical analysis-** Data obtained at the end of study was analysed and represented as tables or figures. Independent' test and chi square test was applied to compare the data between two groups to find out statistical significance of any differences based on p value. All the statistical analysis was done using SPSS software (version 16).

## 3. RESULTS

This study was conducted on a total of 100 cases with CCF and 30 age and sex matched controls.

**Table 1-** Comparison of baseline variables between the group

| Baseline variables | | Cases (n=100) | | Control (n=30) | | P value |
|---|---|---|---|---|---|---|
| | | n | % | n | % | |
| Age (years) | 31-50 | 29 | 29 | 9 | 30 | 0.52 |
| | 51-70 | 53 | 53 | 13 | 43.3 | |
| | 71-90 | 18 | 18 | 8 | 26.7 | |
| | Mean | 59.79±14.31 | | 60.87±14.15 | | |
| Gender | Male | 59 | 59 | 17 | 56.7 | 0.82 |
| | Female | 41 | 41 | 13 | 43.3 | |
| BMI ($kg/m^2$) | <18.5 | 0 | 0 | 0 | 0 | **0.001** |
| | 18.5-24.9 | 27 | 27 | 26 | 86.7 | |
| | 25-29.9 | 65 | 65 | 3 | 10 | |
| | ≥30 | 8 | 8 | 1 | 3.3 | |
| | Mean | 27.17±4.06 | | 23.46±2.59 | | |
| Troponin | Positive | 15 | 15 | 0 | 0 | **0.001** |
| | Negative | 85 | 85 | 30 | 100 | |
| ECG | Normal | 5 | 5 | 25 | 83.4 | **0.001** |
| | Atrial fibrillation | 6 | 6 | 0 | 0 | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | LBBB | 10 | 10 | 1 | 3.3 | |
| | Low voltage complex | 9 | 9 | 0 | 0 | |
| | LVH, LV strain pattern | 14 | 14 | 1 | 3.3 | |
| | RVH, RV strain pattern | 7 | 7 | 0 | 0 | |
| | RBBB | 4 | 4 | 1 | 3.3 | |
| | Coronary artery disease | 43 | 43 | 0 | 0 | |
| | Sinus tachycardia | 4 | 4 | 2 | 6.7 | |
| | P-Pulmonale (poor progression of R wave) | 5 | 5 | 0 | 0 | |
| | Supraventricular tachycardia | 1 | 1 | 0 | 0 | |
| | Multifocal atrial tachycardia | 1 | 1 | 0 | 0 | |
| Echo-cardio-graphy | Normal | 7 | 7 | 27 | 90 | **0.001** |
| | Coronary artery disease | 28 | 28 | 0 | 0 | |
| | Ischemic Cardiomyopathy | 9 | 9 | 1 | 3.3 | |
| | Dilated Cardiomyopathy | 10 | 10 | 0 | 0 | |
| | Concentric LVH | 12 | 12 | 1 | 3.3 | |
| | RV dysfunction | 13 | 13 | 1 | 3.3 | |
| | RV Dysfunction, TR with PAH | 24 | 24 | 0 | 0 | |
| | Rheumatic/Valvular heart disease | 9 | 9 | 0 | 0 | |
| | LV systolic dysfunction | 60 | 60 | 0 | 0 | |
| | Pericardial effusion | 4 | 4 | 0 | 0 | |

In our study, about 53% cases and 43.3% controls belonged to 51 to 70 years of age and majority of cases as well as controls were males (>50%). Cases and controls were comparable with respect to age and gender ($p>0.05$). Majority of cases were overweight or obese with BMI above 25 (73%) whereas significantly higher proportions of controls had normal BMI (86.7%) ($p<0.05$). As observed from table 1, troponin I, ECG abnormalities and echocardiographic abnormalities were documented in significantly higher proportions of cases as compared to controls ($p<0.05$).

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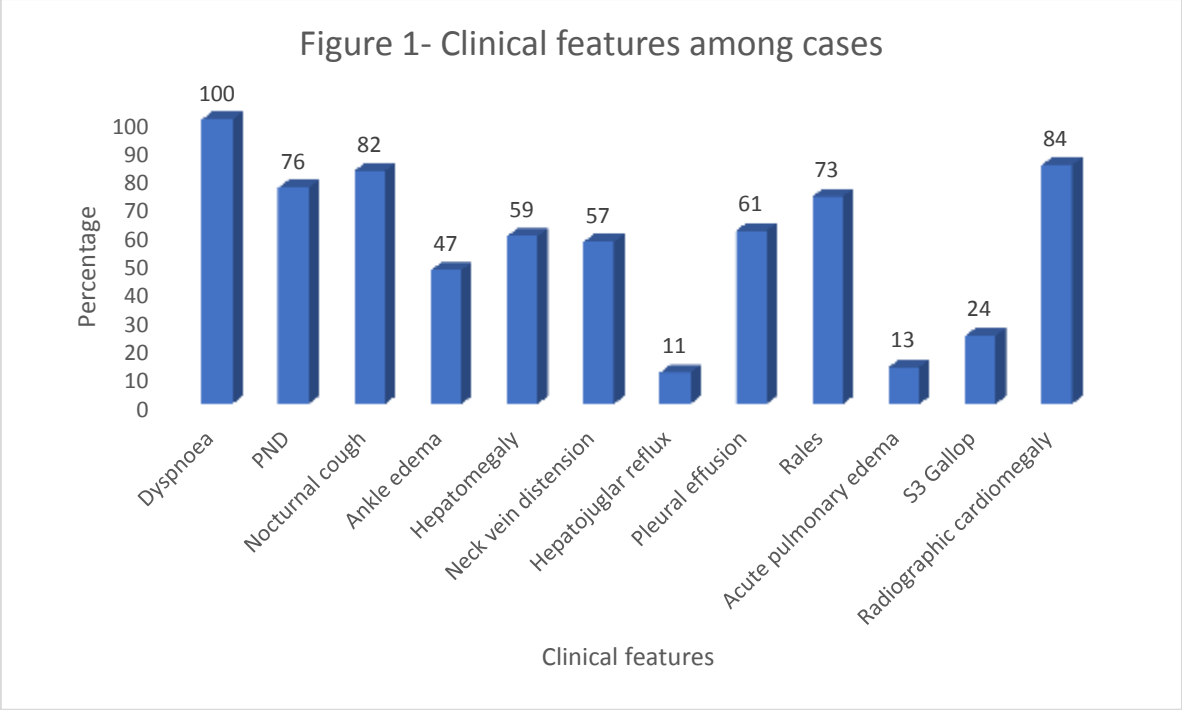


Out of one hundred study cases, all the patients had dyspnea followed by radiographic cardiomegaly (84%), nocturnal cough (82%), PND (76%) and rales (73%) (figure 1).

**Table 2-** NT PRO BNP values in cases presented with CCF as compared to control group

| NT Pro BNP | Cases (n=100) | | Control (n=30) | |
|---|---|---|---|---|
| | n | % | n | % |
| <400 | 4 | 4 | 27 | 90 |
| 401-1000 | 14 | 14 | 3 | 10 |
| 1000-5000 | 29 | 29 | 0 | 0 |
| 5,001-10,000 | 20 | 20 | 0 | 0 |
| 10,001-15,000 | 12 | 12 | 0 | 0 |
| 15,001-20,000 | 7 | 7 | 0 | 0 |
| >20,000 | 9 | 0 | 0 | 0 |
| P value | **0.001** | | | |

NT Pro BNP was found to be raised (>400 ng/ml) in 96% cases and 10% controls and the observed difference was statistically significant ($p<0.05$) (table 2).

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**Table 3**- Association of NT Pro BNP with baseline variables in cases with CCF

| Baseline variables | | NT Pro BNP | | | P value |
|---|---|---|---|---|---|
| | | <400 | >400 | Total | |
| Age (years) | 31-50 | 1 | 28 | 29 | 0.22 |
| | 51-70 | 1 | 52 | 53 | |
| | 71-90 | 2 | 16 | 18 | |
| Gender | Male | 2 | 57 | 59 | 0.709 |
| | Female | 2 | 39 | 41 | |
| BMI ($kg/m^2$) | <25 | 2 | 25 | 27 | 0.29 |
| | ≥25 | 2 | 71 | 73 | |
| Troponin | Positive | 0 | 15 | 15 | 0.089 |
| | Negative | 4 | 81 | 85 | |
| ECG | Normal | 4 | 1 | 5 | **0.001** |
| | Abnormal | 0 | 95 | 95 | |
| Echocardiography | Normal | 3 | 4 | 7 | **0.001** |
| | Abnormal | 1 | 92 | 93 | |

Our study found no significant association of NT ProBNP with age, gender, BMI as well as Troponin I ($p>0.5$), however, ECG as well as echocardiographic abnormalities correlated with NT Pro BNP significantly ($p<0.05$) (Table 3).

## 4. DISCUSSIONS

Heart failure is a common condition with rising prevalence especially in elderly. NT Pro BNP has been described as a new marker for evaluation of heart failure patients.[2] As stated, the high levels of natriuretic peptide have been included in the consensus definition of heart failure.[2] We conducted a case control study to evaluate the role of NT Pro BNP in patients with heart failure. The present study comprised of one hundred cases of congestive cardiac failure and 30 age and sex matched controls. Majority of cases i.e. 53% belonged to age range of 51 to 70 years and we reported male predominance for congestive cardiac failure with male: female ratio of 1.43:1. Our study findings were supported by the findings of Mistry et al, in which majority i.e. 41.7% cases belonged to 50 to 64 years of age and male : female ratio was 1.4:1.[5] Similarly, in a study of Sallah et al, about 60% cases were males and median age of the patients was higher as compared to our study i.e. 74 years.[12] The mean age of patients in a study of Liaquat et al was 54.65±12.5 years and male: female ratio was 1.66:1.[13]

Mean BMI in cases was 27.17± 4.06 $Kg/m^2$ in our study whereas mean BMI in controls was 23.46±2.59 $kg/m^2$, and significantly higher proportions of cases with CCF were either overweight or obese (73%) as compared to controls. Thus, obesity was associated with CCF. The mean BMI in a study of Liaquat et al was somewhat higher (30.1±6.3 $kg/m^2$) in cases with CCF [13] whereas that in COACH study was 27±15$kg/m^2$, supporting our study.[14] However, approximately 30% of the cases in a study of Mistry et al were obese/ overweight,

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with higher BMI in cases with ischaemic heart disease as compared to those with rheumatic heart disease(p=0.005).[5]

Patients with heart failure typically exhibit electrocardiographic abnormalities, and an electrocardiogram in conjunction with an echocardiography can help diagnose the underlying condition associated with heart failure.[15] In the present study out of one hundred cases, five (5%) cases had normal ECG while ninety five (95%) had abnormal in the form of Coronary Artery Disease (43% ), LVH with LV strain pattern (14%),Complete and incomplete LBBB (10%), Low voltage complexes (9%),RVH with RV strain pattern (7%), Atrial fibrillation ( 6%),P pulmonale (5%), Complete and incomplete RBBB (4%), and one(1%) each had supraventricular tachycardia and multifocal atrial tachycardia. Out of thirty controls, 83.34% had normal ECG while 16.66% had it abnormal in the form of Sinus tachycardia (6.66%) and one (3.33%) each case had LBBB, LVH with LV strain pattern and RBBB. With respect to echocardiographic findings, 7% cases with CCF had normal echocardiography findings while 93%cases had abnormal echocardiography findings, most common being left ventricular systolic dysfunction (60%), followed by CAD (28%). However, among controls, 90% had normal echocardiography whereas 10% had abnormalities in Echocardiography in the form of ischemic cardiomyopathy, Concentric LVH and RV Dysfunction in one case each.

In a study of Junior et al, most common ECG findings were non sinus rhythm (98.8%) and LBBB (90.12%) whereas systemic arterial hypertension (82.7%) and coronary heart disease (30.9%) were most common findings suggested by echocardiography.[15] Mistry et al reported arrythmias on ECG in 22.6% cases with HF, abnormal axis in 44.05% (left axis deviation in 20.3%), chamber enlargement in 19.05% cases, 10.71% had LBBB and 16.66% had poor R wave progression. 2D Echo revealed RWMA in 31.3% cases with HF, valves were affected in cases with RHD and 13.5% cases have degenerative changes in valves.[5]

We aimed to assess the role of NT Pro BNP in cases with heart failure and NT Pro BNP levels were found to be normal in 4% cases with CCF whereas they were high in 96% values and among them, ten patients (10%) had very high values ranging from 25,000 to49,000pg/ml. In control group out of thirty cases surprisingly three (10%) cases had abnormal NT pro BNP value ranging from 401 to 1000 pg/ml, while twenty-seven (90%) cases were having expectedly its normal value. The mean NT Pro BNP levels in our study patients were 9310.64±6858.78 pg/ml in cases with HF. Our findings were supported by findings of Liaquat et al, in which mean NT Pro levels in patients with HF was 9045.93±8960pg/ml. [13] Similarly, mean NT Pro BNP levels in patients with HF in a study of Kumar et al was 2589.08 ± 1897.149pg/ml, with much higher levels in severe heart failure as compared to those with milder form of HF (NYHA class II and III). Also, mean NT Pro levels were found to be significantly higher in cases with HF as compared to controls without HF ($p<0.05$).[16] Ozturk et al obtained the overall mean NT- proBNP value of 9741.9 ± 8973 pg/ml (range:245-35,000 pg/ml),the mean NT-proBNP value of the outpatients and hospitalized patients were 6835.9±6935.3 pg/ml (range:245-35000)and 11291.8±9585.5 pg/ml (range:712-35000), respectively.[17]

In the present study, we found no significant association of NT ProBNP levels with age, gender, BMI as well as Troponin ($p>0.05$), whereas we found a significant association of NT Pro BNP levels with ECG and echocardiography findings ($p<0.05$). The findings of present

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study were contrasting to the findings of Dhinakaran et al [18] and Athavale et al [19] in which the authors found a significant association of NT Pro BNP levels with age. The findings of present study were supported by the findings of Li et al, in which NT Pro BNP levels in patients with Echo abnormalities in the form of reduced ejection fraction were significantly higher as compared to those with preserved EF.[20]

Our study findings were also supported by the findings of Goetze et al, where NT-Pro BNP showed a significant association with systolic dysfunction.[21] Among patients with hypertension, Mouly-Bertin et al showed a significant association of NT-Pro BNP with LVH on ECG.[22]

Our study had certain limitations, first due to lack of gold standard method for diagnosis of cardiac diseases, we could not assess diagnostic accuracy of NT-Pro BNP for diagnosis of heart failure. Second, the sample size of study was small and being the facility based cross sectional study, the findings could not be generalized.

## 5. CONCLUSION

NT-Pro BNP is a valuable marker for diagnosis of congestive heart failure and its values correlate well with ECG and Echocardiographic abnormalities. In cases with raised NT-Pro BNP levels, the seriousness and gravity of congestive cardiac failure was varying although not proportionately and had poor prognosis. Cases with normal NT-ProBNP levels have less gravity of CCF and better prognosis. The seriousness, gravity of congestive cardiac failure and higher NT Pro BNP levels warned the urgent need of critical care. Hence NT Pro BNP levels in patients of congestive cardiac failure had a prognostic value too. Thus, NT pro BNP is a good diagnostic and prognostic predictor for congestive cardiac failure.

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