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Comparative Study of Quantitative NT Pro BNP and Troponin T Levels in Patients of Non-Valvular Atrial Fibrillation with Stroke and without Stroke.

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ABSTRACT

Background: AF is an important public health problem and it significantly increases mortality and morbidity in elderly population. This arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world. At present the risk of stroke and the indication for anticoagulation treatment in AF can be estimated by clinical risk factors e.g. the CHADS-2.New markers like troponins and BNP are being investigated for further risk evaluation in AF patients. Aims: To study the quantitative NT pro BNP and Troponin T levels in non Valvular atrial fibrillation patients with stroke and without stroke and prognostic and predictive values of these markers in predicting stroke. **Methods:** The study has been done on patients of chronic non valvular AF (without any history of Rheumatic Heart Disease) in Patna medical college hospital.100 nonvalvular AF patients with stroke, and 100 nonvalvular AF patients without stroke of similar sex and age group matched, underwent for measurement of NT pro BNP, Troponin- T levels determination by quantitative method during May 2015 to October 2016. **Results:** The plasma NT proBNP and Troponin T level were higher in patients with nonvalvular AF with stroke than those without stroke. **Conclusion:** Mortality in study group was significantly higher in stroke group compared to without stroke group.

Keywords: Atrial Fibrillation, Brain Natriuretic Peptide, Stroke.

INTRODUCTION

Atrial fibrillation is of public health importance. It profoundly increases morbidity mortality & health related expenditures. Morbidities include the increased risks of cardiovascular outcomes such as heart failure stroke & the deleterious effects on quality of life, functional status & cognition

Despite good progress in the management of patients with atrial fibrillation (AF), this arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world.

In the people > 75years old the incidence of AF has been reported to increase to 11.6%.[1]

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At present the risk of stroke and the indication for anticoagulation treatment in AF can be estimated by clinical risk factors e.g. the CHADS-2 or the later develop CHA2DS VAS2 score which assigns 1 points each for a history of congestive heart failure, hypertension, diabetes mellitus vascular disease, age ≥65 and sex category (female sex) and 2 points for the age ≥75years and the previous stroke/TIA.[1]

Recently cardiac troponin, a sensitive indicator of myocardial damage, was identified as an independent marker of increased risk of stroke, other cardiovascular event, and mortality in patients with AF by the use of contemporary assay. The availability of the next generation of high sensitivity troponin assay, which enables the detection of very low level of troponin concentration with high precision, might, improved the prognostication substantially in several patient populations.

In searching of biomarkers of a predisposition to AF, studies shows diathesis towards this arrhythmia might be reflected in abnormalities of natriuretic peptide axis, as atrial structure and function are central to both the afferent efferent limb of this endocrine pathway. The natriuretic peptide hormones are secreted in response to several stimuli, including intra-cardiac pressure, and have become popular candidate for the non-invasive assessment of cardiac dysfunction. The level of NT-pro Brain Natriuretic Peptide is increased in patients with various heart diseases such as congestive heart failure, dilated

cardiomyopathy, hypertrophic cardiomyopathy, hypertensive heart disease, and lone AF.

Contrary to earlier theories that BNP is mainly secreted by the ventricular myocardium, it was reported recently that the left atrium, not the left ventricle, is the main source of BNP in patients with AF. The proposed mechanisms are high frequency of atrial myocyte contraction and local atrial inflammation. The main stimulus for their synthesis and release is wall stress, which produces a rapid gene transcription response. The primary regulation for production is at the synthesis level, not at the secretion level.

NT-pro Brain Natriuretic peptide level does not correlate either with the duration of AF or with left atrial dimensions. How quickly it increases after the onset of AF has not been studied. In the field of AF a multitude of biomarkers are available and new ones are constantly being identified and assessed. Biomarkers may increase the understanding of the pathogenesis of AF as well as refine future risk prediction. Some markers appear to reflect the pathophysiologic process for development of AF, while others may simply be suited as markers of risk for future cardiovascular events.[2]

Over the last decade, major developments have led to significant changes in the antithrombotic management of patients with AF. A risk score in form CHADS was developed to start preventive measures for stroke. But new data have emerged on what were previously referred to as less well validated risk factors for stroke, namely female sex, age of 65 to 74 years, and vascular disease.

Although simple the CHADS score does not include many common risk factor, and its limitations have recently been highlighted. Patients classified as low risk by CHADS in its original validation study have stroke rate of 1.9%/year, which is close to the criterion of a cardiovascular event rate of 20% over 10 years for primary prevention strategies, (e.g. the use of statins).

A recent analysis also confirms that patients with a CHADS score of 0 were not all low risk, and anticoagulation decisions based simply on a CHADS score of 0(the category recommended to have no antithrombotic therapy or aspirin in some guideline) may be insufficient to avoid stroke in patients with AF.

Troponin T in AF

Recent studies also have been done for the role of cardiac troponin in risk stratification in atrial fibrillation. Probable hypothesis is that atrial fibrillation produces myocardial stretch injury implicated in raised levels of cTnT.

Troponin release in AF patients may be connected to several of these mechanisms associated with myocardial dysfunction, apoptosis, inflammation, and fibrosis in the atrial and ventricular musculature, as well. The higher proportion of patients with troponin elevation in permanent AF as an indicator of increased AF burden and a more advanced cardiac disease supports this hypothesis and also the relation to major bleeding events.[6]

Troponin T in Stroke[3]

Although elevated cTnT serum level is relatively infrequent in acute ischemic stroke patients .There are existing studies of troponin elevations in patients with acute ischemic stroke.

In one study elevated levels of cTnT are detected in 5%-36% of AIS patients. In another study (n=416) its raised levels are detected in 10.8% of patients.

The reason suggested for their raised levels is because damage to cortical areas controlling autonomic functions (i.e. insular cortex). Which lead to surge in catecholamine level and may induce left ventricular dysfunction.

Because data are very limited the interpretation of these studies remains unclear in clinical practice.

NTproBNP in Stroke [4-7]

NT pro BNP level may also increase in stroke patients without AF. But their increase in stoke patients signifies that the stroke is of cardio embolic in origin as compared to other subtypes of stroke.

After searching for further similar studies it was found that many studies do not exclude the presence of possible confounding variables like renal failure heart failure and ischemic heart disease, which can also lead to raised NT-proBNP levels.

There are following studies which suggest the role of NTproBNP and cTnT in prevention of stroke in AF patients.

Daisuke watanabe etal demonstrated the role of natriuretic peptide levels indicating thromboembolism in very elderly patients with non valavular AF.[8]

AIM

To study the quantitative NT pro BNP and Troponin T levels in non Valvular atrial fibrillation patients with stroke and without stroke and prognostic and predictive values of these markers in predicting stroke

MATERIALS AND METHODS

The study has been done on patients attending medical outdoor and or hospitalised for chronic non valvular AF (without any history of Rheumatic Heart Disease) in Patna medical college hospital.

100 nonvalvular AF patients with stroke, and 100 nonvalvular AF patients without stroke of similar sex and age group matched, underwent for measurement of NT pro BNP, Troponin- T levels determination by quantitative method during May 2015 to October 2016.

During the admission or outdoor visit Prothrombin time, INR, Serum Electrolyte, Electrocardiography

Transthoracic Echocardiography, Chest x ray, Liver function test, Serum Creatinine, Blood Urea, USG whole abdomen, CHA2DS2VAS risk score will be done for each patients and other parameters will also be evaluated regarding other systemic symptoms.

Inclusion Criteria and Exclusion Criteria

Patients attending medical outdoor or hospitalised for AF with stroke and without stroke, of similar age group and sex matched.

Patients having Valvular heart disease , Structural heart disease , Active liver disease ,Creatinine clearance <30 ml/min ,Symptomatic congestive heart failure NYHA class II or more Overt organ failure or malignancy were excluded from study.

Statistical Analysis

Statistical analysis was done by using percentages, mean, median values, Standard Deviation, Standard Error, $\chi 2$-test (chi-square test) (with Yates correction), one way analysis of variance test and proportion tests with the help of SPSS statistical software package version 10.0 for Windows. The level of significance used was 0.05 level for the corresponding degree of freedom to draw the inference. A p-value <0.05 was considered statistically significant and a p>0.05 was considered as not statistically significant.

RESULTS

Table 1: Sex distribution in different group.

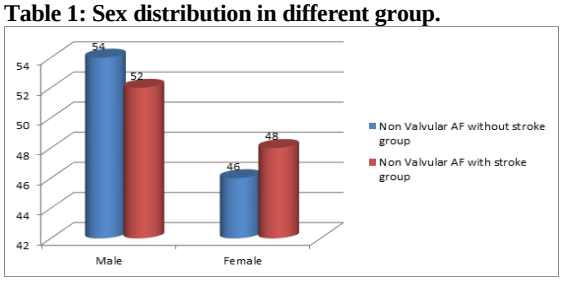


Table 2: Age distribution of Non Valvular AF without stroke group and with stroke group.

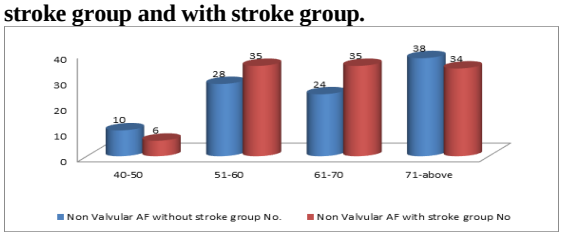


Table 3: Comparison of Hypertensive patients in Non Valvular AF without stroke group and with stroke group

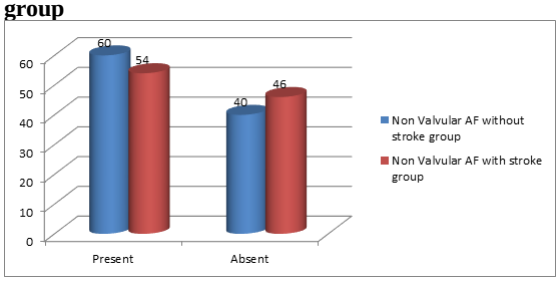
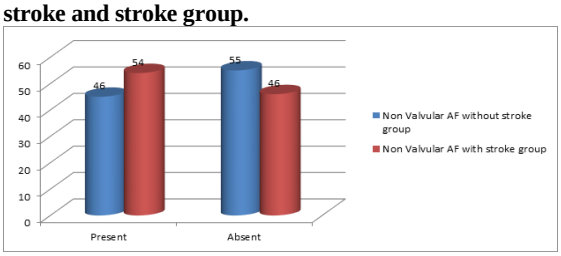


Table 4: Diabetes mellitus in Non Valvular AF without stroke and stroke group.



Distribution of Diabetes mellitus was insignificant at P=0.2.

Table 5: Follow up (12 month) in cases (Non Valvular AF without stroke group and with stroke group)

Age group (yrs)	Non Valvular AF without stroke group		Non Valvular AF with stroke group		'P' Value
	No.	%	No.	%	
Survive	90	90	73	73	0.006
Death	10	10	24	24	
Total	100	100	100	100	

Mortality in study group was significantly higher at p=0.006

Table 6: Distribution of cases according to Troponin-T level of Non valvular AF without stroke group and Non valvular AF with stroke group, cut off point was 0.014µg/l based on previous studies.

Group	>0.014	< = 0.014	Median	'P' value
Non valvular AF without stroke group	70	30	0.016	0.09
Non valvular AF with stroke group	82	18	0.112	

Median of Troponin T in study group significantly higher at p=0.09 than control group.

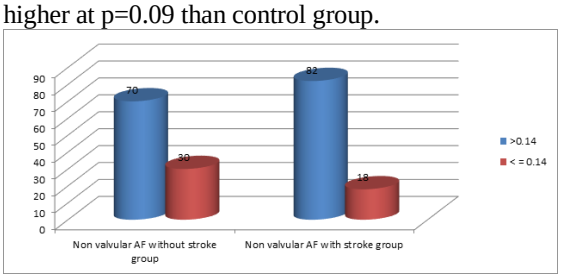


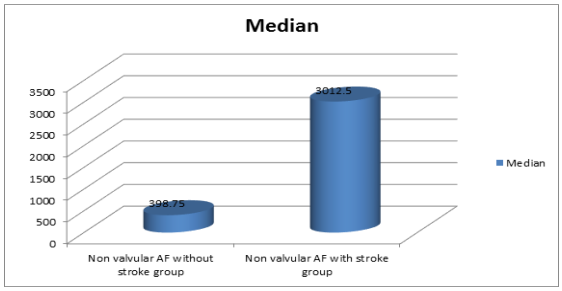
Table 7: Distribution of cases according to NT Pro BNP level of Non valvular AF without stroke group and Non valvular AF with stroke group

Group	Median
Non valvular AF without stroke group	398.75
Non valvular AF with stroke group	3012.5

In the control group median was 398.75 and in the study group median was 3012.5.

Table 8: Troponin T quartiles for stroke group.

Mortality in Troponin T quartiles for stroke group				
	Q1 (<.015)	Q2 (.015-.112)	Q3 (.112-.238)	Q4 (>.238)
No. Of Person	18, (18%)	32, (32%)	22, (22%)	28, (28%)
Mortality	1, (5%)	2, (6%)	6, (27%)	18, (64%)

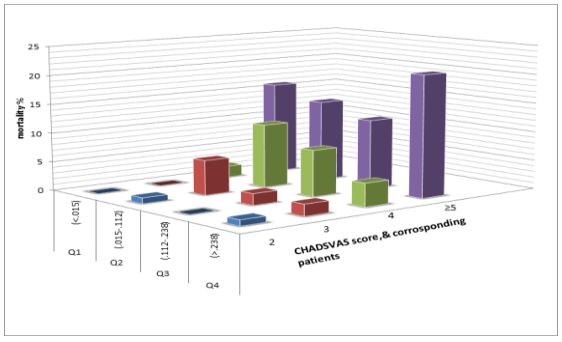


In the top quartile mortality was 64% compared to only 1% in lowest quartile values are significant in comparing these two quartiles at p=0.006.

Table 9: CHA2DS2-VASc score, and mortality in different quartiles of troponin T.

	Q1 (<.015)	Q2 (.015-.112)	Q3 (.112-.238)	Q4 (>.238)
NO.OF Person	18, (18%)	32, (32%)	22, (22%)	28, (28%)
Female	12, (66%)	17, (53%)	05, (22%)	14, (50%)
DM	18, (100%)	10, (31%)	11, (50%)	15, (53%)
HTN	17, (94%)	16, (50%)	12, (54%)	15, (55%)
CHF	01, (5%)	08, (25%)	05, (22%)	10, (35%)
Age Above 75	1, (0.5%)	6, (18%)	7, (31%)	12, (42%)
CHA2DS2 VAS 2	0	1	0	1
3	0	6	2	2
4	2	11	8	4
5	8	10	7	12
6	7	3	5	4
7	1	1	0	4
8	0	0	0	1

Patients were analysed for the risk factors in different quartiles of cTnT, table showing numbers and percentage wise distribution in different quartile.



There were higher numbers of patients of CHA2DS2-VASc score ≥5 in each quartile with higher number of mortality in top quartile

Table 10: Mortality in NT proBNP quartiles for stroke group

	Q1 <2199.25	Q2 2199-3012.5	Q3 3012.5-3383	Q4 >3383
No. Of Person	23, (23%)	27, (27%)	25, (25%)	25, (25%)
Mortality	3, (13.04%)	4, (17%)	5, (20%)	15, (60%)

Mortality was highest in top quartile 60% compared to 13.04% in lowest quartiles. On comparing both the quartiles values were significant at p=0.02

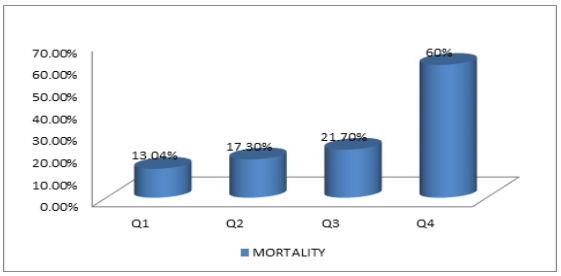
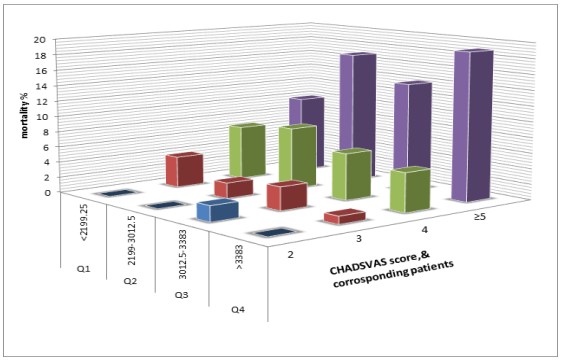


Table 11: CHA2DS2-VASc score and mortality in different quartiles of NTproBNP

	Q1 <2199.25	Q2 2199-3012.5	Q3 3012.5-3383	Q4 >3383
NO.OF Person	23, (23%)	27, (27%)	25, (25%)	25, (25%)
Female	13, (56%)	13, (56%)	08, (32%)	14, (56%)
DM	11, (47%)	13, (48%)	14, (56%)	16, (64%)
HTN	17, (73%)	15, (55%)	11, (44%)	17, (68%)
CHF	06, (26%)	10, (37%)	06, (24%)	07, (28%)
Age above 75	3, (13%)	7, (25%)	6, (24%)	10, (40%)
CHA2DS2 VAS 2	0	0	2	0
3	4	2	3	1
4	7	8	6	5
5	7	10	8	11
6	3	5	6	3
7	0	2	0	4
8	0	0	0	1

Patients of study group were analysed for risk factors according to four quartiles of NTproBNP, table showing percentage and number wise distribution in four quartiles.



There were higher numbers of patients of CHADS2VA2S score ≥5 in each quartile with higher mortality in top quartile

Table 12: Percentage of Death in common numbers of patients in Top quartile and lowest quartile of both biomarkers.

	Top quartiles in both markers	Lowest quartile in both markers
common % of patients	20%	19%
Death	72%	12.5%

Mortality was much higher in patients who were common to top quartiles of both biomarkers. (P=0.1)

DISCUSSION

The study was done on 100 patients of nonvalvular AF with stroke attending outpatient department or hospitalised.Another One hundred age and sex matched patients of atrial fibrillation without stroke constituted the control. NT-pro BNP and Troponin T level were estimated in both the groups on the admission day. All the patients were followed up for one year.

Patients were stratified according to age starting from 40 onward, 51 onward, 61 onward and 71 and above. In study group 34% were in the range of 71 and above, 39% were in the range of 61-70 years, 21% were in the range of 51-60 years and 6% were in the range of 40-50 years. In the control group 38% were in the range of 71 and above 24% in the range of 61-70 years, 28% were in the range of 51-60 years, and 10% were in the range of 40-50 years. There was no significant difference in both the group (p=.53) [Table 2]. In the present study design in both the groups majority of the patients were above 60 years i.e. 73% in study groups and 62% in control groups. .

Hypertension was found in 60 % in study group as compared to 54% in control group. The finding were statistically insignificant at p=0.39 [Table 3].

Diabetes mellitus was present in 54% of study group, and 45% in control group [Table 4]. The difference were statistically insignificant at (p=0.5)

Congestive heart failure another risk factor was present in 24% of study group and 20% in control group. The difference were statistically not significant at p=.49

After following the patients for one year, mortality in study group were 24% and 10% in control group. [Table 5] The difference were statistically significant at p=0.006.

In previous studies it has been found that Troponin T >.014µg/l is associated with higher risk of morbidity and mortality in CAD and CHF patients So in the present study also patients were divided into two groups based on troponin T levels, ≤ 0.014 µg/l in one group and > 0.014µg/l in another group. Troponin T was high in 82% in study group and 70% in control group. The difference was statistically significant p=0.04. The median value of Troponin T in study population was 0.112 compare to 0.016 in control group.

In the present study the mean value of NT-proBNP was higher in stroke group (3012.5pg/ml) as compared to (398.7pg/ml) in non-stroke group [Table 6]. Daisuke Watanabe et al (n=74), studied in all AF patients and found the median value of BNP were 288pg/ml this is similar to our control patients. Ziad Hijazi etal has observed higher proBNP level in all AF patients (n=18201) the median value of NT-proBNP was 718pg/ml. Ziad Hijazi may have selected patients with multiple risk factors so have led to higher median levels of NTproBNP compared to our control group.

In table 6 and 7 it has been observed Troponin T and NTproBNP levels are higher in AF stroke patients. To evaluate the relationship of these biomarkers level with future prognosis, the study group was further sub-divided into four quartiles as per NTproBNP levels and Troponin T level [Table 8-11]. And relationship with mortality was evaluated.

In NTproBNP group,there are 24 patients in first quartile (<2199.25), mortality was 13.04% in that group. Mortality progressively increased from first quartile to top quartile. In the second quartile it was 17.30%, in the third quartile it was 21.70%, and in the top quartile it was 60%. In the top quartile mortality was statistically significant compared to lowest quartile (p=0.006). [Table 12] In a study by Ziad Hijazi (n=6189), it was observed that mortality was higher in the top quartile 2.30%/year compared to 0.92%/year in the lowest quartile of NTproBNP even in AF without stroke.

The patients in various quartiles of NT proBNP levels were also evaluated for associated risk factors [Table13]. In the first quartile DM was present in 45% of patients, hypertension was present in 70% of patients; CHF was present in 25% of patients. 53% patients were female, and 13% were age >75 years.

In the second quartile (2199.25-3012.5) there were 26 patients, with 50% patients were having DM, 57% were having hypertension, and 19% were having CHF. 48% patients were female and 25% were age >75 years.

In third quartile (3012.5-3383) there were 25 patients, with 56% were having DM, 44% were having hypertension, 24% were having CHF, 32% were female and 24% were age >75.

In the fourth quartile (>3383) there were 25 patients with 64% were having DM, 68% were having hypertension, 28% were having CHF, 56% were female and 40% were age >75 years.

In all quartiles of NT proBNP various risk factors are more or less evenly distributed so not contributing to variation in proBNP level. so increased mortality with high proBNP has an independent role in prognosticating the patients

Ziad Hijazi et al n=14821, had observed in AF without stroke grp and in that group also he had similar observation. in their first quartile(<387) mortality was 0.92%, hypertension was present in 82.3% DM was present in 23% and CHF was present in 18.9%, in the second quartile (387-800) hypertension was present in 78%, DM was present in 21.7%, CHF was present in 27.3%. In the third quartile (801-1402) hypertension was present in 77.3%, DM was present in 21.5%, and CHF was present in 30.6%. In the fourth quartile >1402 hypertension was present in 76%, DM was present in 19.1% and CHF was present in 43.3%.

Patients were further sub divided according to cTnT quartiles [Table10-11].

In the first quartile (<0.15) there were 18 patients mortality was 5%. It was also observed that mortality progressively increases from first to top quartile. In the second quartile mortality was 6%, it was 27% in third quartile and in the top quartile it was 64%. Mortality was statistically significant in the top quartile compared to lowest quartile (p=0.02). Similar mortality pattern also observed by Ziad Hijazi etal, has done study on AF patients without stroke in that study mortality was also higher in top quartile 4.24% compare to 0.46% in lowest quartile.

In the first quartile all the patients were diabetic, 94% having hypertension, 5% were having CHF, 66% patients were female, and 0.5% were age >75 years.

In the second quartile (0.015-0.112) there were 32 patients, mortality was 6%, hypertension was present in 50%, DM was present in 31% of patients, CHF was present in 25% of patients, 53% patients were female and 18% were age >75 years.

In the third quartile (0.112-0.238) there were 22 patients mortality was 27%, hypertension was present in 50% of patients, DM was present in 51% of patients, and CHF was present in 22% of patients. 22% were female and 31% were age >75.

In the fourth quartile >0.238, there were 28 patients, mortality was 50%, hypertension was present in 55%, DM was present in 53%, CHF was present in 35%, 50% were female and 42% were age >75 years.

In comparison to previous study by Ziad Hijazi et al n=14821, in their first quartile(<387) mortality was 0.92%, hypertension was present in 82.3% DM was present in 23% and CHF was present in 18.9%, in the second quartile (387-800) hypertension was present in 78%, DM was present in 21.7%, CHF was present in 27.3%. In the third quartile (801-1402) hypertension was present in 77.3%, DM was present in 21.5%, and CHF was present in 30.6%. In the fourth quartile >1402 hypertension was present in 76%, DM was present in 19.1% and CHF was present in 43.3%.

NTproBNP and cTnT levels rise during renal failure. To rule out influence of renal disturbance in the study, Patients were evaluated for kidney function. In the study group the mean value of serum creatinine and blood urea was 0.856 and 31.72 respectively, and in control group their values were 0.844 and 29.72 respectively. In comparing both the group the values were not significant (p>0.05). So rise in NTproBNP and cTnT levels are not influenced by any disturbance in renal function.

Patients were also evaluated for any advantage for combining both NTproBNP and cTnT. [Table 12]. Those who were common to both in the top quartiles of cardiac biomarkers, mortality was 72% and those were common to both in the lowest quartile of both cardiac biomarkers, mortality was 12.5%. p=0.1.

So combining both biomarkers in prognosticating may have added advantage, but our sample size is small and larger study should be planned.

CONCLUSION

The present study conducted on 100 patients of Atrial fibrillation without any structural or Rheumatic heart disease with stroke and 100 similar patients of same age group and gender matched without stroke, attending outpatient department or hospitalised. Quantitative estimation of biomarkers NT-pro BNP and Troponin T level was done on the admission day, and both groups of patients were followed for one year.

There was no significant difference between the two groups in terms of the serum creatinine level or incidence of heart failure and so plasma NT pro BNP level not influenced by cardiac or renal parameters. Also age, gender ratio, hypertension, diabetes mellitus, doesn't influence the result of the present study.

In the present study it was observed that,

I. The plasma NT proBNP level was higher in patients with nonvalvular AF with stroke than those without stroke.
II. Troponin T levels are higher in patients with nonvalvular AF with stroke than those without stroke.
III. Mortality in study group was significantly higher in stroke group compared to without stroke group.
IV. In the stroke group patients were divided into four quartiles according to NTproBNP and Troponin T levels and it was observed that mortality was higher in top quartiles with comparing to lowest quartiles. So NTproBNP and Troponin T level may help in prognosticating in patients of AF with Stroke.
V. Among the patients who were in the top quartile of both biomarkers mortality was higher compared to those who were in the lowest quartiles of both biomarkers. So using both these biomarkers could have additive advantage.

Present study indicates that the levels of NTproBNP and cTnT in atrial fibrillation with stroke have prognostic value regarding mortality. There are limitations of this study, with the smaller study design, does not allow final conclusions concerning the optimal cut-off value of cardiac biomarkers.

The present study has prognostic value and added advantages on combining both NTproBNP and Troponin T in AF patients with stroke, but because of smaller study design further studies in the field of AF with stroke are warranted.

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