Bangladesh Medical Res Counc Bull 2024; 50: 104-110 DOI: 10.3329/bmrcb.v50i2.76857

RESEARCH PAPER

Association of Serum FT_3 with Severity of Heart Failure and it's Correlation with NT-proBNP

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Abstract

Background: Heart failure is a global health emergency affecting millions of people worldwide and is increasing in prevalence. NT-proBNP is a hormone that is a marker of severity and prognosis of heart failure. Thyroid hormone has an important regulatory impact on the heart. Altered thyroid function specially triiodothyronine and increase NT-proBNP are highly prevalent in heart failure patients without apparent thyroid diseases.

Objectives: To evaluate the association of serum free T_3 (FT_3) with heart failure severity and its correlation with NT-proBNP as a potential marker.

Methods: A cross-sectional analytical study was conducted at the Department of Biochemistry, Sir Salimullah Medical College (SSMC), over a 12-month period from March 2022 to February 2023. A total of 110 clinically diagnosed heart failure subjects were enrolled in this study and divided into two groups. Among them 55 heart failure patients with NT-proBNP >2000 pg/ml were included in group I and 55 heart failure patients with NT-proBNP 125-2000 pg/ml were included in group II. Written informed consent was obtained from patients and detailed history, clinical examinations were done followed by serum FT_3, serum TSH and serum NT-proBNP were determined by laboratory investigations. Data was collected using a semi-structured questionnaire and Statistical analysis was done by using SPSS version 22.0.

Results: In this study, more than one third (34.5%) of patients had low serum FT_3 (<2.3 pg/ml) in group I and 16.4% in group II. The difference was statistically significant ($p<0.05$). A total of 28 patients had low FT_3, where 2(7.1%) were in group I and 26(92.9%) were in group II among them 18(64.3%) patients had NT-proBNP level >4000 pg/ml. The TSH level did not differ significantly between the groups ($p>0.05$).

Conclusion: Serum FT_3 had an inverse relation with NT-proBNP in patients with heart failure. As low FT_3 is associated with severe heart failure with high NT-proBNP, low FT_3 could be a potential marker for heart failure severity.

Keywords: Heart failure patients, serum FT_3, serum TSH, serum NT-proBNP.

Introduction:

Heart failure is a chronic progressive disorder in which the heart muscle is unable to pump enough blood to meet the body's needs for blood and oxygen. The incidence of HF in developed countries is approximately 1-2% in adult population at age 60-69 years with prevalence rising to ≥10% among persons 70 years of age.[1,2] The HF rate is increasing in developing countries and this rising trend has also been observed in people who lead urban lifestyle.[3] The projections are worrisome since it is expected >8 million people will have this condition by 2030 and the prevalence is increasing by 46%.[4]

Thyroid hormone is required for normal growth and development as well as regulating metabolism in adults.[5] These hormones are thyroxine (T_4) and 3,32 ,5-triiodo-L-thyronine (T_3), which are synthesized and secreted from thyroid follicular cells.[6] Thyroid release >85% T_4 into bloodstream, certain cells transform it into T_3 through a process called de-iodination.[7] Thyroid hormones, specially T_3 exhibit a variety of effects on the heart and peripheral vascular system.[8] In severe illness there is drop of serum T_3 levels and circulating TSH & T_4 usually remains within normal range.[9] These changes are due to induction of D3 enzyme activity and reduction of D1 and D2 activation.[10] D3 catalyzes

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the conversion of T_4 to reverse triiodothyronine (rT_3) and the conversion of T_3 to 3,32 -diiodothyronine (T_2).[11] These typical changes in T_3 concentrations were called the low T_3 syndrome and is associated with a worse prognosis in heart failure.[9,12]

NT-proBNP is an important biomarker in heart failure.[13] It is well known that volume expansion, myocardial stretch, is a key factor of its secretion, while many neurohumoral factors also induce its secretion.[14] Increased NT-proBNP level in heart failure reflected volemia and disease severity.[15]

Suppression of thyroid axis function in heart failure contributes to impairment of cardiac pumping activity.[16] That increases myocardial stretch which further increases NT-proBNP levels.

In this context, the current study has planned to evaluate the association of serum FT_3 with severity of heart failure and its correlation with NT-proBNP. It may give an idea that low FT_3 concentration plays a critical role in disease progression. Low FT_3 may serve as a valuable biomarker for risk stratification, aiding clinicians in identifying high-risk patients, as well as appropriate measures that can prevent the consequences of heart failure.

Materials and Methods:

The study was a cross-sectional analytical study conducted in the Department of Biochemistry, Sir Salimullah Medical College for a period of twelve months, extending from March 2022 to February 2023. The study was conducted among 110 clinically diagnosed heart failure patients aged up to 74 years who were admitted within 6 hours in the department of cardiology in Sir Salimullah Medical College (SSMC) and National Institute of Cardiovascular Diseases (NICVD) during the study period. Patients with previously diagnosed cases of thyroid disorders or treated with thyroid medication or history of renal impairment & dialysis, liver cirrhosis, pulmonary hypertension or other lung problems, cancer, or suffering from severe infection (sepsis), or subjects with history of dopamine or steroids intake were excluded. Sampling was selected purposively after obtaining informed consent from the patients before enrollment in the study. Before starting the data collection, all patients were described about the study objective and details procedure of the study. They were clearly informed that this participation is voluntary, and they had the freedom to withdraw themselves from the study at any stage. Data was collected by history taking, clinical examination and recorded on a standard questionnaire by the researcher. Serum NT-proBNP were done. The grouping of the study subjects were done after estimating NT-proBNP. Group-I included heart failure subjects with NT-proBNP > 2000 pg/ml and group-II included heart failure subjects with NT-proBNP 125-2000 pg/ml. Serum FT_3 level was observed between these two groups. Additional serum TSH was also done. Prior to conducting the study, ethical approval was obtained from the Institutional Review Board (IRB) of SSMC. All data was checked, coded and entered in standard statistical software version-22.0. An unpaired t test was performed to observe the mean age, any significant difference between the mean value of blood pressure and EF, the mean values of serum TSH between the study groups. The Chi square test was done to observe the status of serum FT_3 and the association between serum FT_3 with NT-proBNP in HF patients. Pearson's correlation was used to show the correlation between FT_3 and NT-proBNP in the study groups. The *p*-value of <0.05 was considered statistically significant.

Results:

A total of 110 clinically diagnosed heart failure subjects were enrolled in this study in two groups- group I and group II. Among them 55 heart failure patients with NT-proBNP > 2000 pg/ml were included in group I and 55 heart failure patients with NT-proBNP 125-2000 pg/ml were included in group II.

An Unpaired-t test was done to observe the mean age was 65.05±9.94 years in group I and 62.44±9.26 years in group I. The difference was not statistically significant ($p>0.05$) between two groups (Table I).

An Unpaired - t test was done to measure the mean SBP was 103±12.8 mmHg in group I and 101.9±12 mmHg in group II. The mean DBP was 66.9±10.2 mmHg in group I and 66.1±10.4 mmHg in group II. The difference was not statistically significant ($p>0.05$) between two groups. The mean EF was 40.8±11.7% in group I and 52.7±12.5% in group II. The difference was statistically significant ($p<0.05$) between two groups (Table II).

A Chi-square test was done to measure the level of significance. It was observed that more than one third (34.5%) of patients had low serum FT_3 (<2.3 pg/ml) in group I and 16.4% in group II. The difference was statistically significant ($p<0.05$) between two groups (Table III).

An Unpaired-t test was done to measure the mean serum TSH was 3.07±1.0 mIU/L in group I and 3.37±0.62 mIU/L in group II. All (100%) of patients had belonged to normal (0.55-4.78 mIU/L) serum TSH level in both groups. But the difference was not statistically significant (p>0.05) between two groups (Table IV).

A Chi-square test was done to measure the association between serum FT_3 with NT-proBNP in heart failure patients. A total of 28 patients had found low FT_3, where 2(7.1%) in 125-1200 pg/ml NT-proBNP, 8(28.6%) in 1200-3999 pg/ml and 18(64.3%) in 4000->35000 pg/ml NT-proBNP. Patients with low FT_3 level were found

Table I: Distribution of the study patients according to age (N=110)

Age(years)	Group I (n=55) [NT-proBNP >2000]	Group II (n=55) [NT-proBNP 125-2000]	*p*-value
Mean±SD	65.05±9.94	62.44±9.26	0.157^{ns}
Range (Min-Max)	35-74	33-74	

Values are presented as mean±SD.
p-value was determined by Unpaired-t test, ns= not significant.

Table II: Status of the study patients according to blood pressure and EF (N=110)

	Group I (n=55) [NT-proBNP >2000] Mean±SD	Group II (n=55) [NT-proBNP 125-2000] Mean±SD	*p*-value
SBP (mmHg)	103±12.8	101.9±12	0.642^{ns}
Range (Min-Max)	90-130	85-130	
DBP (mmHg)	66.9±10.2	66.1±10.4	0.684^{ns}
Range (Min-Max)	50-95	50-95	
EF (%)	40.8±11.7	52.7±12.5	0.001^{s}
Range (Min-Max)	21-68	28-72	

Values are presented as mean±SD
p-value was determined by Unpaired-t test, s= significant and ns= not significant.

Table III: Distribution of the study patients according to serum FT_3 (N=110)

Serum FT_3 (pg/ml)	Group I (n=55) [NT-proBNP >2000]		Group II (n=55) [NT-proBNP 125-2000]		*p*-value
	n	%	n	%	
Low (<2.3)	19	34.5	9	16.4	0.028^{s}
Normal (2.3-4.1)	36	65.5	46	83.6	

Results are presented as frequency and percentage
p-value determined by Chi-square test, s= significant.

Table IV: Status of the study patients according to serum TSH (N=110)

Serum TSH (mIU/L)Normal (0.55-4.78)	Group I (n=55) [NT-proBNP >2000]	Group II (n=55) [NT-proBNP 125-2000]	*p*-value
Mean±SD	3.07±1.0	3.37±0.62	0.061^{ns}
Range (Min-Max)	1.04-4.72	1.84-4.32	

Values are presented as mean±SD
p-value was determined by Unpaired-t test, ns= not significant.

Table V: Association between serum FT_3 with NT-proBNP (N=110)

Serum FT3	NT-proBNP (pg/ml)						*p*-value
	125-1200 (n=38)		1201-3999 (n=35)		4000->35000 (n=37)		
	n	%	n	%	n	%	
Low	2	7.1	8	28.6	18	64.3	0.001[s]
Normal	36	43.9	27	32.9	19	23.2	

Results are presented as frequency and percentage
p-value determined by Chi-square test, s= significant.

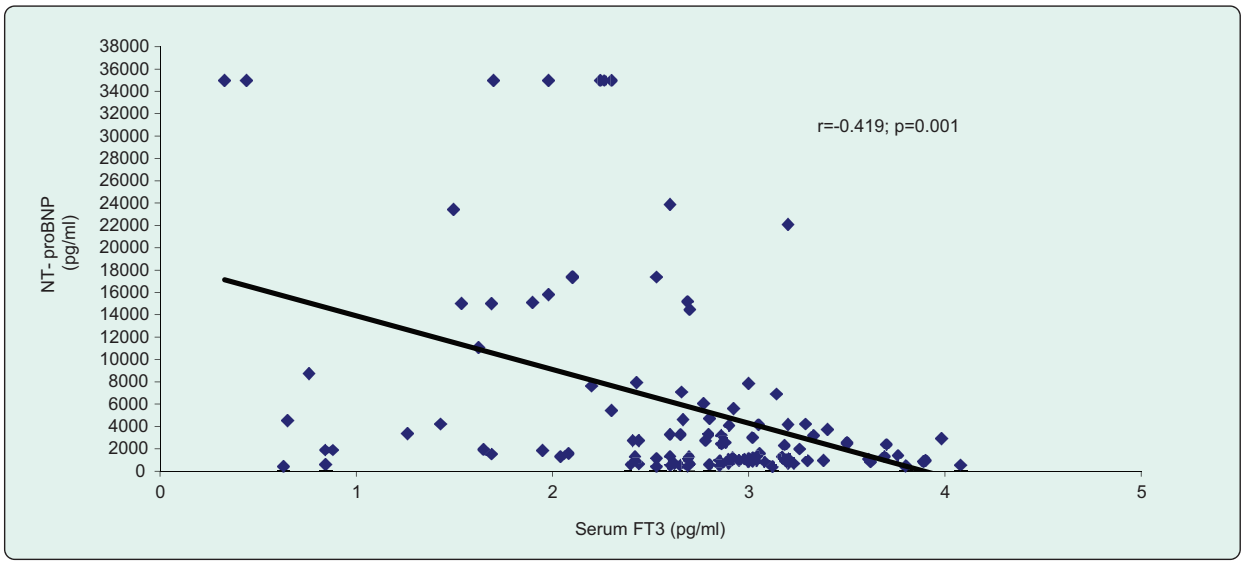

Figure 1: Scatter diagram showing negative pearson correlation between serum FT_3 with NT-proBNP.

more in higher NT-proBNP and the difference was statistically significant (p<0.05) (Table V).

The pearson correlation test showed a negative correlation between serum FT_3 with NT-proBNP (r= - 0.419; r^2= 0.18; p=0.001) (Figure 1).

Discussion:

A total of 110 subjects were included based on predefined enrollment criteria. Among them 55 were heart failure patients with NT-proBNP > 2000 pg/ml and 55 were HF patients with NT-proBNP 125-2000 pg/ml. This study was conducted in the department of Biochemistry, Sir Salimullah Medical college, Dhaka from March' 22 to February' 23 to assess the relation between FT_3 and NT-proBNP in patients with heart failure.

In this study the mean age was 65.05±9.94 years in group I and 62.44±9.26 years in group I. It was evident from the current study that heart failure prevalence increases from middle to old age.[17-19]

In the present study Mean SBP was (103±12.8 Vs 101.9±12) and mean DBP was (66.9±10.2 Vs 66.1±10.4) mmHg almost similar in both groups.[20,21] Mean EF% was lower in group I than group II. There was a significant negative correlation observed between NT-proBNP level.[11]

In accordance with the present study low serum free triiodothyronine (<2.3 pg/ml) was observed more than one third (34.5%) of patients in NT-proBNP >2000 pg/ml than 16.4% in patients with NT-proBNP 125-2000 pg/ml. Increased NT-proBNP related with low free triiodothyronine level.[16, 22-25] Low thyroid hormone concentration, mainly low serum FT_3 concentration, is a common finding in patients with non-thyroidal illnesses, including cardiac diseases like heart failure.[11]

The current study showed that the mean serum TSH was 3.07±1.0 in group I and 3.37±0.62 mIU/L in group II. It was observed that all the patients had belonged to normal TSH (0.55-4.78) level in both groups.[9, 26-27] Normal TSH levels were common in patients with non-thyroidal illnesses.

In this study low FT_3 was observed 7.1% in NT-proBNP125-1200 pg/ml, 28.6% in NT-proBNP 1200-3999 pg/ml and 64.3% in 4000->35000 pg/ml NT-proBNP of heart failure patients. It was evident that the percentage of low FT_3 was significantly higher in high NT-proBNP HF patients. Low free triiodothyronine was associated with severe heart failure patients with high NT-proBNP level.[11, 28-29]

In the present study, Pearson's correlation test was done to observe the relation between serum FT_3 levels with NT-proBNP in heart failure patients. It showed a significant negative correlation between free triiodothyronine level with NT-proBNP in study subjects (p= <0.001).[11,16] Increased N-terminal pro B-type natriuretic peptide level is associated with high cardiac related morbidity and mortality in patients with HF. So, this inverse relation suggests that low FT_3 is a strong predictive marker for severe heart failure patients.[23,30-32] In this study the co-efficient of correlation was r=-0.419 and co-efficient of determination was r^2= 0.18. That means high NT-proBNP is only 18% that is due to low FT_3.

Although our study also has some limitations such as small sample size and the absence of serial evaluation of serum TT_3 and serum FT_4 were not analyzed due to financial constraints of the study, the study population was selected from a few selected hospitals in Dhaka city with limited time span, so the result of the study may not reflect the exact picture of the country. However, this study suggests that low triiodothyronine state may produce a hypothyroid-like-syndrome that contributes to the worsening or exacerbation of the intrinsic cardiac diseases.

Conclusion:

In conclusion, serum FT_3 inversely correlated with NT-proBNP in patients with severe heart failure. Low FT_3 plays a critical role in the progression of heart failure and could potentially serve as a biomarker for risk stratification. The present study may be useful for the clinicians for risk stratification of severe heart failure patients. Additional study is needed to determine the prognosis and specific treatment with FT_3 supplementation that should be prioritized in high-risk heart failure patients.

Acknowledgements:

The authors would like to express their sincere gratitude to the guide, teachers, and colleagues for their help in data analysis and manuscript revision and editing.

Conflict of interest: No conflict of interest.

Funding: Partially financially supported by Bangladesh Medical Research Council (BMRC).

Ethical Clearance: Ethical clearance taken from the Institutional Review Board (IRB) of Sir Salimullah Medical College.

Submit Date: 14 October, 2024

Accepted: 23 February, 2025

Final Revision Received: 26 February, 2025

Publication: July 2025

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