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Diagnostic Value of N Terminal Pro B Type Natriuretic Peptide (NT-pro BNP) in Cardiac Involvement in Patients with Beta-Thalassemia

Noor Mohammad Noori [1], *Alireza Teimouri [1], Nahid Anvari [2]

[1] Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.
[2] Medical School, Zahedan University of Medical Sciences, Zahedan, Iran.

Abstract

Background

Heart failure is a major cause of death in thalassemia. The study aimed to determine the diagnostic value of N Terminal Pro B Type Natriuretic Peptide (NT-pro BNP), to early diagnose the cardiac involvement in beta- thalassemia major patients.

Materials and Methods

80 thalassemia patients aged 7 to 18 years old (patients group), and 80 healthy age and gender matched controls were enrolled in the case-control study. Patients were selected from those attending to the clinic of Aliasghar hospital, Zahedan-Iran. They were subjected to echo-Doppler tissue and conventional examination for both right and left heart function. Data were analysis using SPSS 18.0 software.

Results

NT-pro BNP increased in patients compared the controls (P<0.001). Some of conventional echocardiography left heart's functions such as deceleration time (DT), Simpson's Ejection fraction (EF), Myocardial Performance Index (MPI), were significantly higher in patients, and fractional shortening (FS), EF and the ratio of the early (E) to late (A) ventricular filling velocities (Peak E/ Peak A), were lower. DTI left heart's functions of ICT, Isovolumic relaxation time (IRT), and MPI were higher in patients, too. Conventional echocardiography right heart's functions, peak E, ET, MPI, and peak E/ peak A, were different from patients to controls. Conventional echocardiography, Left atrial in diastole LAd (P=0.01), Left ventricular diameter at systole (LVDS) (P=0.004), Simpson's left ventricular diastolic dysfunction LVDd (P=0.004), and relative wall thickness (RWT) (P=0.022), were different in patients groups based on of NT- pro BNP cut of point 100.

Conclusion

From the study concluded that left heart dysfunctions had more correlation with NT-proBNP compared the right heart functions.

Key Words: Beta-Thalassemia, Cardiac Involvement, Children, NT-pro BNP.

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***Corresponding Authors:**

Alireza Teimouri: M.Phil, Ph.D, Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.

Email: alirezateimouri260@gmail.com

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1- INTRODUCTION

Beta-thalassemia is a group of blood inherited disorders that comprise and causes severe anemia from early childhood with approximately 60,000 to 100,000 newborns around the world (1, 2). The disease is common in Mediterranean countries, the Middle East, Central Asia, India, Southern China, the Far East and the countries along the coast of North Africa and South America (2). Beta-thalassemia major is a form of the severe disease and the patients' survival depends on repeated lifetime blood injections. If a regular blood transfusion and hemoglobin concentration is maintained between 9.5 and 10.5 preserved, the growth of the patients will be normally continued until 12 years old (3). Iran with about 25,000 thalassemia patients and three million carriers would be considered as the highlighted area with variation in different parts. The prevalence in the Persian Gulf and the Caspian Sea regions is more than 10 percentage (4).

Sistan and Baluchestan province of Iran, with about 2 million population located in the Southeastern Iran, has thalassemia gene frequency varied from 4 to 10 percent in which deals about high numbers of patients with major beta thalassemia who are receiving regular health services such as blood transfusion (5). Complications of iron overload in children included of growth retardation, lack or maturity delay, heart disease, liver diseases, Endocrine disorders and other complications included of splenomegaly, chronic hepatitis with infection, venous thrombosis and osteoporosis (6-9). Cardiac involvements by iron deposition are the most important complications due to iron overload in beta- thalassemia, and can be considered as a leading cause for 71% mortality in these patients (10). Some of heart abnormalities in children with thalassemia major are as follow; left ventricular systolic dysfunction, diastolic dysfunction, pulmonary hypertension, functioning disorders, and cardiac arrhythmias (11). Natriuretic Peptide (NP), has been considered as a diagnostic biomarker for cardiovascular diseases, and it contains of B-type natriuretic peptide (BNP), prohormone brain natriuretic peptide (pro BNP). In comparison, N Terminal Pro B Type Natriuretic Peptide (NT-pro BNP), is more stable and has a longer half-life about 2 hours in compare to BNP (12). Increasing levels of NT-pro BNP in thalassemia patients with left ventricular diastolic dysfunction is directly related to age and it is a good biomarker for early diagnosis of left ventricular dysfunction. In the early phases of the cardiac involvement the level of NT-pro BNP increases before an increase in diastolic pressure and there is a strong relationship between plasma levels of NT-pro BNP and iron overload (13). Reported that has been observed significant relationships between NT-pro BNP, and some diastolic dysfunctions (14). It is approved that an increase level of NT-pro BNP, can be used as a tool for primary detection of cardiac hemosiderosis, and is confirmed iron chelation therapy, which may reverse iron-induced cardiomyopathy (15).

If the patients treated with chelation, they would still be at risk in secondary abnormal heart tissue with iron deposition, and this event has been remained as a major cause of death in thalassemia patients. Incidence of pulmonary hypertension in patients with Hb S beta-thalassemia (β/S thalassemia), is similar to patients with sickle cell disease (SCD), and the serum of NT- pro BNP, is a strong indicator for patients with β/S thalassemia with pulmonary hypertension, and it may be used for diagnosis of pulmonary hypertension (16). Patients with major beta- thalassemia faced to an increase in the level of NT- pro BNP, when diastolic left ventricular dysfunction increased.

High serum of NT- pro BNP is related to levels of E' / E in Doppler tissue imaging (DTI), in patients with major thalassemia (17). Patients with thalassemia major need frequent blood transfusions, and if not treated their iron overload, they would be at risk of cardiac dysfunction. Accordance what was mentioned above, this study aimed to determine the diagnostic value of NT-pro BNP to early diagnose the cardiac involvements in major beta- thalassemia patients.

2- MATERIALS AND METHODS

2-1. Methodology

This case-control study was performed in pediatric cardiac center with collaboration of center for specific diseases in Ali Asghar hospital, Zahedan city, Sistan and Baluchestan province from August 2015 to July 2016. Eighty patients with major beta- thalassemia aged 7 to 18 years were diagnosed based on hemoglobin electrophoresis and enrolled to the study. Same matched age and gender numbers of healthy volunteers were randomly selected from who referred to the hospital for routine checkup to serve as control subjects. Sample size was based on the cost, ethical limitation especially for controls and age consideration.

2-2. Criteria

After detecting obvious valvular disease in patients, rhythm abnormality, structural, active infection, other systemic inflammatory diseases and renal insufficiency, were considered as exclusion criteria for both groups.

2-3. Echocardiography and laboratory measurements

Major proceedings were performed on both patients and controls such as medical history, physical examination, chest X-ray and Electrocardiogram (ECG), before echocardiography and echocardiography was performed by same cardiologist. Echocardiography was performed 48-72 hours after packed red blood cell transfusion on patients by same pediatric cardiologist with using of My lab 60 with transducer 3, 8 (made in Italy). For having high precision in information echocardiography repeated 3 cycles in 2D, M-Mode, Doppler and tissue Doppler imaging methods and the average was considered. Echocardiogram applied in participants without breath holding, and view was taken in the mitral valve surface in parasternal position. Simpson EF: EF was calculated in the apical chamber, LVDd: left ventricular end-diastolic dimension, a: is the time of interval between the end and the start of trans-mitral and trans-tricuspid flow, AT: Acceleration time, DT: deceleration time, Peak E: early mitral and tricuspid valve flow velocity, Peak A: late mitral and tricuspid valve flow velocity, LAd: Diameter of LA in Diastole, Aod: Diameter of Aorta in Diastole, LAs: Diameter of LA in Systole, Aos: Diameter of Aorta in Systole, Et: ejection time (for Aorta and Pulmonary), PWDD: posterior wall dimension in diastole, IVSD: interventricular septal dimension in Diastole, IVSS: interventricular septal dimension in systole, EF: ejection fraction, FS: fractional shortening, LVM: left ventricular mass, RWT: relative wall thickness, LVMI: left ventricular mass index, were measured using conventional echocardiography of the left side were estimated from three cardiac cycles. Myocardial performance index (MPI), isovolumic relaxation time (IRT), isovolumic contraction time (ICT) of both sides, were measured with pulsed Doppler echocardiography (2).

The sample volume was positioned at the tips of the tricuspid and mitral valve leaflets in the apical four-chamber view to enable the measurement of (a): that is the time of interval between the end and the start of trans-mitral and trans-tricuspid flow. The sample volume was thereafter relocated to the left ventricular outflow tract just below the aortic valve (apical five-chamber view), so as to measure (b): which is the left ventricular ejection time. The right ventricular outflow velocity pattern was also recorded from the parasternal short-axis view with the Doppler sample volume positioned just distal to the pulmonary valve for the measurement of (b). Myocardial Performance Index (Tei Index), was calculated as: a-b/b = IRT + ICT/ET.

The left ventricular mass index (LVMI), was also calculated by the following formula:

LVM (g) = 0.8 (1.04 [LVEDD + PWTD + IVSTD)^3- LVEDD ^{3}]) + 0.6. And LVMI (g/m^2) = LVM / 2.7 (g/m^2).

All the parameters in the above formula were measured in the M-mode view and in diastole and were utilized for left ventricular mass evaluation (2, 18). Relative Wall Thickness (RWT), was calculated as 2 times PWD divided by the LVEDD (19). Doppler tissue echocardiography (DTI), was another method that was performed from the apical four-chamber view and a 3 mm pulsed Doppler sample volume was placed at the level of lateral mitral annulus.

Myocardial velocity profiles of the lateral tricuspid annulus and lateral mitral annulus, were obtained by placing the sample volume at the junction of the tricuspid annulus and the right ventricle (RV), free wall and at the junction of the mitral annulus and LV posterior wall, respectively. With this modality, the recorded values, were the early (E), and late (A), diastolic mitral and tricuspid annular velocities, and the ratio of E/A. Right ventricle and left ventricle MPI, was obtained by dividing the sum of Isovolumic Relaxation time (IRT), and Isovolumetric contraction time (ICT), by the ejection time (ET) (MPI = (ICT + IRT)/ET) (**Figure.1**).

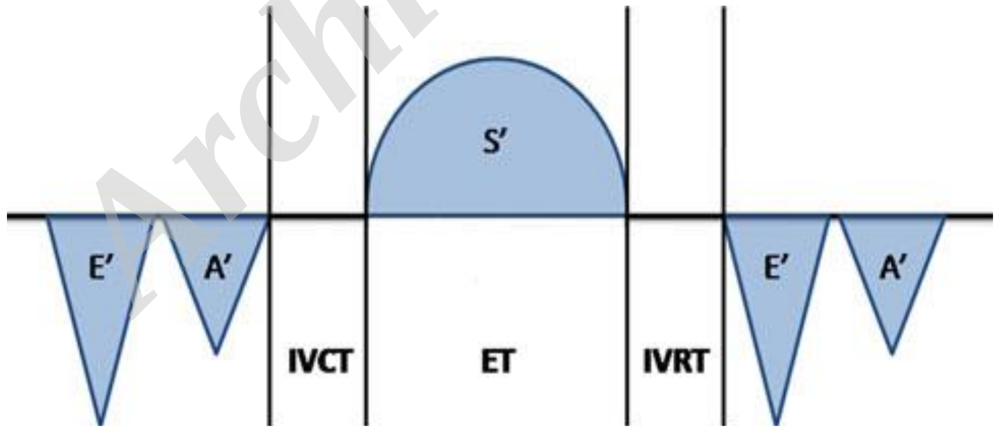

Fig.1: Diagram of Doppler Tissue Echocardiography waves: S': systolic wave; E': early diastolic wave; A': late diastolic wave (20).

Our participants were weighted using RASA Mark made in Islamic Republic of Iran by error factor of 100 grams. In addition, their heights were measured in the standing position with a scale ruler.

Three milliliter of blood was taken from all patients at 8.00 AM after an overnight fasting. The sample was centrifuged at 3,000 rpm/min for 10 minutes at 5 °C.

Separated serum was kept in -70cc refrigerator until NT-pro BNP measuring. The samples transferred to the biochemistry library of Zahedan University of Medical Sciences with considering the cold chain circumstances and then 250 microns isolated serum samples selected for measuring the levels of NT-pro BNP by ELISA kit.

2-4. Ethical Approval

Consent form was obtained from the patients, controls or their guardians after the study approval. The study was approved as a thesis for the degree of pediatric specialty by the Ethics Committee of Zahedan University of Medical Sciences, Zahedan, Iran (ID number: 6798). The written informed consent was obtained from all participants.

2-5. Statistical analysis

All statistical procedures were performed using SPSS (Statistical Package for Social Sciences) Windows version 18.0 (SPSS Inc, Chicago, IL, USA). Data were summarized by mean ± standard deviation (SD). Shapiro-Wilk W test was performed for testing normality.

Statistically significant differences between two groups of continuous variables were determined by using the independent samples t-test and Mann-Whitney U test, as appropriate. A p-value < 0.05 was considered statistically significant.

3- RESULTS

In this study, 160 participants were enrolled with equal ratio in case and controls. The gender distributions in patients were 47.5 and 52.5 for girls and boys, respectively. In the controls the trends of gender distribution were 38.8% and 61.2 % for girls and boys. The Chi-square test showed no significant differences in gender distribution (P=0.26). Normality test were used for studied variables for patients and participants (**Table.1**). Table.1 revealed that all variables had not normal distribution in the case of participants, when some of them had in patients such as LVDD (K.S = 0.06; P=0.20), peak E (K.S=0.05; P=0.20) and DT (K.S=0.08; P=0.20), in conventional echocardiography left heart.

Parametric and non-parametric test were applied for normal and non-normal variables. In accordance with the **Table.2**, NT-pro BNP was much higher in cases (140.47± 131.12), compared the controls (34.47± 47.61), so that this difference was significant (P<0.001). Controls' mean age was 15.43 ± 5.68 years and in patients were 16.55 ± 5.41 years old. The results showed that mean age in controls was not significantly lower (P=0.093). Anthropometric indices such as height (P<0.001), weight (P=0.001), were in a significant lower levels in patients, so that height and weight means were 159.01±14.21 vs. 152.19±10.44, and 48.63 ± 12.80 vs. 42.09± 9.47, respectively in control compared the patients group.

Table.3 shows a comparison between patients and controls regarding left heart function based on conventional and tissue Doppler echocardiography performances. Conventional echocardiography left heart's functions such as a (the time of interval between the end and the start of trans-mitral and trans-tricuspid flow)

(P=0.002), Deceleration Time (DT) (P=0.001), Simpson EF (P=0.001), MPI (P<0.001), were higher in patients compared with controls, and FS (P<0.001), EF (P<0.001), and Peak E/ peak A (P<0.001), were lower significantly. The DTI left heart's functions namely a (P<0.001), ICT (P<0.001), IRT (P<0.001), and MPI (P<0.001), were higher in patients compared with controls.

Table.4 shows a comparison between Patients and controls regarding right heart function based on conventional and tissue Doppler echocardiography performances. Conventional echocardiography right heart's functions such as a (P<0.001), Peak E (P=0.006), ET (P<0.001), MPI (P<0.001), and peak E/peak A (P=0.001), were different in patients compared with controls. The DTI left heart's functions namely a (P<0.001), ICT (P<0.001), IRT (P<0.001), and MPI (P<0.001), had same trends in patients compared with controls.

Based on the cut of point 100 for NT-pro BNP, patients were categorized in two groups. The results of t-test showed that the majority of heart functions were higher in patients with NT-pro BNP higher than 100, but amongst them only two LVDD (P=0.038), and Simpson LVDS (P=0.017), were significant (**Table.5**). Nonparametric Mann-Whitney test was applied for non-normal variables in both left and right heart functions (**Tables 6 and 7**).

Functions measured by conventional echocardiography such as LAd (P=0.01), LVDS (P=0.004), Simpson LVDD (P=0.008), and RWT (P=0.022), were significantly different in patients groups. Only one function MPI, measured by Doppler tissue echocardiography had significantly different values between patients who categorized accordance NT-pro BNP cut of point 100. All right functions measured by two mentioned methods were similar.

4- DISCUSSION

The present study revealed that NT-pro BNP was much higher in patients with major beta-thalassemia when height and weight were lower. Totally compared to controls, in patients, conventional echocardiography left heart's functions such as deceleration time, EF by Simpson, MPI were higher when FS, EF and E /A, were lower.

The Doppler tissue echocardiography left heart's functions such as ICT, IRT and MPI, were higher in patients. Conventional echocardiography right heart's functions such as AT, E, ejection time, MPI and E/A, were different in patients. The Doppler tissue echocardiography right heart's functions ICT, IRT, and MPI, had same trends. Patients divided in two groups based on the cut-off-point 100 of NT-pro BNP. LVDD and Simpson LVDS, had significantly different values between control and patient groups. Left heart functions measured by conventional echocardiography such as Lad and LVDS were higher in patients with NT-pro BNP > 100; also, Simpson LVDD and RWT, were higher in patients with NT-pro BNP =<100. From left heart functions that measured by Doppler tissue echocardiography, only MPI was varied between patients, significantly higher in patients with NT-pro BNP > 100. All right functions measured by two mentioned methods were similar.

Balkan et al. and Kremastinos et al. found that the levels of NT-pro BNP serum were higher in patient which was in same lines with our results (13, 14). In Balkan study, clinical, laboratory and echocardiographic findings were analyzed in matched age and gender thalassemia patients and controls. From the study resulted that LV dimensions were increased in the patients, while there was no differences in EF and FS. In the present study demonstrated that the two late functions in left heart were different in groups of participants. From Balkan et al. study was resulted that diameters of LA, LV mass index (LVMI), early and late mitral flow velocity were increased in patients compared to controls, E/A ratio and DT, were same between two groups (14). In the present study same results observed expect LVMI, peak A velocity, E/A, and DT with dissimilar outcomes. In the present study resulted that ICT, IRT, and MPI by DTI, were higher in patients when Balkan concluded that IRT was significantly shorter in patients in the case of MPI by DTI the result of the present study confirmed by Noori et al. (18).

Kremastinos et al. conducted a study on β-thalassemia patients to find the predictive value of B-type natriuretic peptides in detecting latent left ventricular diastolic dysfunction. From the study resulted that NT-pro BNP was higher in patients same our result. Echocardiographic Doppler findings such as Left ventricular dimensions and volumes were higher in patients (13), these results would be confirmed in compared with our results. Fractional shortening and ejection fraction did not differ between patients and controls; while in our study, both were higher in patients. In their study E/A ratio was higher in patients, while the ratio was higher in controls in the present study, E and deceleration time (DT), was decreased strongly in patients when in our study, E was much higher in controls and DT was lower in controls.

Noori et al. in a study on patients with major-thalassemia revealed that the majority of echocardiography findings of left and right heart were higher in patient group. From the study resulted that E/A, peak A and Simpson LVDD, were significantly higher in patients and DT was lower when EF, FS and Peak A, were similar. These functions were related to the left heart. In the right heart, ICT and Peak velocity were increased in patients. The results from the present study, were similar and confirmed comparatively by Noori's findings (21). Abdelmoktader and Azer assessed the left ventricular functions in children with Thalassemia major and controls by tissue Doppler imaging and conventional echocardiography respectively, and reported that tissue Doppler imaging had a stronger power to detect the variations. They reported that LA, LVDD, LVDS, IVSD, PWDD, EF, and FS, were varied from patients to controls, so that, EF and FS were lower in patients and others, were higher. These results in comparisons with our findings, are approximately similar. In comparison with our study, we considered that NT- pro BNP because of its higher effect and one of BNP derivation. The majority of studies revealed that in patients with beta- thalassemia major, they first encounter with diastolic dysfunction.

Gong found out the relationship between BNP levels and left ventricular diastolic functions in thalassemia patients and proposed higher BNP levels as a predictor in patients with LV dysfunctions (22). Fathy et al., concluded that BNP levels increased with severity of left ventricular diastolic dysfunction in patients with thalassemia major. The results of the study, confirmed our results in same pattern with a light different in the type of biomarker (23).

Ibrahim et al., demonstrated that the majority of DTI, and conventional findings, were higher in patients compared the controls. The resulted that left MPI were lower significantly in patients and vice versa in right MPI, but no significant. The results of the present study showed that all the mentioned findings were significantly higher in favor of patients in left and right hearts with DTI, and conventional echocardiography (24).

Ragab et al., conduct a study on 25 multi-transfused beta- thalassemia major patients and 20 controls, to diagnose the value of echocardiography in asymptomatic beta- thalassemia major children. In this study conventional echo revealed that Aorta, LA, LVEDD, LVESD, and peak E velocity, were higher significantly in patients compared to controls. But TDI finding showed that ICT and IRT increased patients. In compare with the present study, the DTI finding were similar and conventional finding were comparable with a slight confirmation, so that Ao and peak E velocity, were dissimilar, LA, LVEDD and LVESD, were similar too (25).

Garadah et al., attempted to find the NT-pro BNP serum level and echocardiographic tissue Doppler abnormalities in patients with beta-thalassemia major; and a comparison performed with an age-matched control. Patients had higher IVSD, PWDD, LVDD, peak E velocity, E/A ratio and shorter DT. The mean serum NT-pro BNP in patients was same to our study (17) which was significantly higher, and for the finding of EF and FS, was not significantly different. Ozyoruk et al. aimed to assess Doppler echocardiographic and tissue Doppler in beta-thalasemia patients with high and normal NT-pro BNP levels.

NT-pro BNP levels were significantly increased in patients same our results. The LVDD and LVM index values were significantly decreased in patients with high NT-pro BNP compared to normal (26). In the present study, IRT, ICT and MPI, were detected by DTI method that was different with Ozyoruk study that they found an increase of (E/E′) in patients with high NT-pro BNP levels.

4-1. Limitations of the study

The study limitation was lack of Proper Corporation by participants especially controls.

5- CONCLUSION

In conclusion, according to our result, elevated a strong association between NT-pro BNP and a few echocardiographic indices of myocardial dysfunctions in young Beta- thalassemia patients; while there was a strong increase of NT-pro BNP levels in thalassemia patients there was strong correlation between NT-pro BNP levels and some cardiac parameters especially in left heart by conventional and tissue Doppler echocardiography. Therefore increased levels of NT-pro BNP can be used as a marker for diagnosis the severity of some cardiac involvements in young thalassemia patients.

6- ABBREVIATION

NP: Natriuretic Peptide,
BNP: B-type natriuretic peptide,
Pro BNP: prohormone brain natriuretic peptide,
NT-pro BNP: N Terminal Pro B Type Natriuretic Peptide,
SCD: sickle cell disease,
DTI: Doppler tissue imaging,
ECG: Electrocardiogram,
EF: Ejection fraction,
LVDd: Left ventricular end-diastolic dimension,
LVDS: Left ventricular diameter at systole,
AT: Acceleration time,
DT: deceleration time,
Peak E: Early mitral and tricuspid valve flow velocity,
Peak A: Late mitral and tricuspid valve flow velocity,
LAd: Diameter of Left atrial in Diastole,
Aod: Diameter of Aorta in Diastole,
LAs: Diameter of LA in Systole,

Aos: Diameter of Aorta in Systole,
ET: Ejection time (for Aorta and Pulmonary),
PWDD: Posterior wall dimension in diastole,
IVSD: Interventricular septal dimension in diastole,
IVSS: Interventricular septal dimension in systole,
EF: Ejection fraction,
FS: Fractional shortening,
LVM: Left ventricular mass,
RWT: Relative wall thickness,
LVMI: Left ventricular mass index,
MPI: Myocardial Performance Index (Tei Index),
RWT: Relative Wall Thickness,
DTI: Doppler tissue echocardiography,
RV: Right ventricle,
IRT: Isovolumic relaxation time,
ICT: Isovolumetric contraction time.

7- AUTHORSHIP CONTRIBUTIONS

Noor Mohammad Noori and Nahid Anvari designed the study. Data collection and entering in SPSS performed by Nahid Anvari. Data analyzed by Alireza Teimouri as well as writing the primary manuscript and corresponding author. The critical revision supervised by Noor Mohammad Noori and Alireza Teimouri.

8- CONFLICT OF INTEREST: None.

9- ACKNOWLEDGMENTS

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Table-1: Variables Normality distribution

Functions	Patients		All participants		Functions	Patients		All participants	
	Test value	P- value	Test value	P-value		Test value	P- value	Test value	P- value
NT-Pro BNP (pmol / L)	0.278	<0.001	0.267	<0.001	IVSS (cm)	0.115	0.011	0.126	<0.001
Height(cm)	0.095	0.068	0.08	0.015	LVDS (cm)	0.445	<0.001	0.415	<0.001
Weight (kg)	0.111	0.017	0.122	<0.001	PWDS (cm)	0.43	<0.001	0.417	<0.001
Age(yr)	0.152	<0.001	0.14	<0.001	Simpson LVDS(ml)	0.069	0.200	0.08	0.014
Left conventional echocardiography					EFI%)	0.307	<0.001	0.311	<0.001
Simpson EF(%)	0.105	0.029	0.081	0.012	FS(%)	0.239	<0.001	0.269	<0.001
LVDD(cm)	0.059	0.200	0.079	0.016	Simpson LVDD(ml)	0.301	<0.001	0.26	<0.001
a(ms)	0.159	<0.001	0.082	0.010	Left Doppler tissue echocardiography				
AT(ms)	0.155	<0.001	0.167	<0.001	MPI	0.134	0.001	0.132	<0.001
DT(ms)	0.081	0.200	0.099	0.001	a (ms)	0.251	<0.001	0.162	<0.001
Peak E(cm/s)	0.054	0.200	**0.162**	<0.001	ICT(ms)	0.137	0.001	0.08	0.014
Peak A(cm/s)	0.089	0.181	0.153	<0.001	IRT(ms)	0.225	<0.001	0.187	<0.001
Aod (cm)	0.46	<0.001	0.43	<0.001	Right conventional echocardiography				
LAd (cm)	0.457	<0.001	0.425	<0.001	A(ms)	0.093	0.087	0.14	<0.001
Aos(cm)	0.448	<0.001	0.425	<0.001	AT(ms)	0.138	0.001	0.148	<0.001
Las (cm)	0.45	<0.001	0.43	<0.001	DT(ms)	0.085	0.200	0.084	0.007
Et (ms)	0.109	0.020	0.112	<0.001	Peak E(cm/s)	0.181	<0.001	0.123	<0.001
IVSD (cm)	0.086	0.200	0.103	<0.001	PeakA (cm/s)	0.165	<0.001	0.116	<0.001
LVM(g)	0.083	0.200	**0.097**	**0.012**	ET (ms)	0.119	0.007	0.108	<0.001
RWT	0.113	0.013	0.09	0.003	MPI	0.166	<0.001	0.1	0.001
MPI	0.102	0.039	0.068	0.07	Peak E/ Peak A	0.095	0.071	0.1	0.001
Peak E/ Peak A	0.087	0.200	0.091	0.002	Right Doppler tissue echocardiography				
LAd/AOd	0.071	0.200	0.097	0.001	a (ms)	0.213	<0.001	0.289	<0.001
Las/Aos	0.147	<0.001	0.082	0.011	ICT(ms)	0.159	<0.001	0.145	<0.001
LVMI(g/m^2)	0.083	0.200	**0.093**	**0.01**	IRT(ms)	0.224	<0.001	0.13	<0.001
PWDD(cm)	0.162	<0.001	0.137	<0.001	MPI	0.166	<0.001	0.1	0.001

NT-proBNP: N-terminal prohormone of brain natriuretic peptide, Simpson EF : EF was calculated in the apical chamber, LVDD: left ventricular end-diastolic dimension, a: is the time of interval between the end and the start of trans-mitral and trans-tricuspid flow, At: Acceleration time, Dt: deceleration time, Peak E: early mitral and tricuspid valve flow velocity, Peak A: late mitral and tricuspid valve flow velocity, LAd: Diameter of LA in Diastole, Aod: Diameter of Aorta in Diastole, Las: Diameter of LA in Systole, Aos: Diameter of Aorta in Systole, Et: ejection Time (for Aorta and Pulmonary), PWDD: posterior wall dimension in diastole, IVSD: interventricular septal dimension in Diastole, IVSS: interventricular septal dimension in systole, EF: ejection fraction, FS : fractional shortening, LVM: left ventricular mass, RWT: relative wall thickness. MPI: myocardial performance index, LVMI: left ventricular mass index, ICT: Isovolumic contraction time, IRT: Isovolumic relaxation time.

Table-2: Case-control comparison of some basic variables

Variables	Groups	Mean	SD	Median	Mean Rank	Sum of Ranks	MW	P-value
NTproBNP (pmol / L)	Control	34.47	47.61	21.70	47.71	3816.5	576.5	<0.001
	Case	140.47	131.12	78.25	113.29	9063.5		
Ag (year)	Control	15.43	5.68	15.00	74.36	5949.0	2709.0	0.093
	Case	16.55	5.41	18.00	86.64	6931.0		
Height (cm)	Control	159.01	14.21	160.00	93.31	7465.0	2175.0	<0.001
	Case	152.19	10.44	150.00	67.69	5415.0		
Weight (kg)	Control	48.63	12.80	46.50	92.59	7407.0	2233.0	0.001
	Case	42.09	9.47	40.00	68.41	5473.0		

NT-Pro BNP: N-terminal prohormone of brain natriuretic peptide, SD: standard deviation.

Table-3: Case-control comparison of some conventional and Doppler tissue echocardiographic left heart functions

Variables	Groups	Mean	Std. Deviation	Mean Rank	Sum of Ranks	Median	Mann-Whitney U	P-value
Conventional								
a (ms)	Control	421.510	39.284	69.330	5546.500	422.000	2306.500	0.002
	Case	435.580	45.936	91.670	7333.500	433.000		
AT (ms)	Control	60.460	6.426	78.850	6308.000	61.000	3068.000	0.642
	Case	61.150	8.021	82.150	6572.000	61.000		
DT (ms)	Control	133.900	20.919	67.790	5423.500	133.000	2183.500	0.001
	Case	148.150	27.265	93.210	7456.500	144.000		
Peak E (cm/s)	Control	99.163	18.887	84.560	6765.000	100.150	2875.000	0.267
	Case	95.498	18.543	76.440	6115.000	96.000		
Peak A (cm/s)	Control	48.426	8.894	70.620	5649.500	49.800	2409.500	0.007
	Case	55.030	15.505	90.380	7230.500	55.000		
Aod (cm)	Control	2.385	0.402	79.170	6333.500	2.480	3093.500	0.716
	Case	3.528	5.032	81.830	6546.500	2.400		
Lad (cm)	Control	2.477	0.453	62.050	4964.000	2.400	1724.000	<0.001
	Case	4.157	5.927	98.950	7916.000	2.890		
Aos (cm)	Control	2.270	0.387	81.930	6554.500	2.250	2925.500	0.498
	Case	3.214	4.462	77.010	6006.500	2.240		
Las (cm)	Control	1.613	0.287	59.970	4797.500	1.570	1557.500	<0.001
	Case	2.885	4.307	99.530	7763.500	1.910		
ET (ms)	Control	261.190	29.932	91.050	7284.000	256.000	2356.000	0.004
	Case	249.050	20.976	69.950	5596.000	250.000		
IVSD (cm)	Control	0.750	0.138	85.570	6845.500	0.760	2794.500	0.166
	Case	0.728	0.113	75.430	6034.500	0.730		
LVDD(cm)	Control	4.273	0.450	70.480	5638.000	4.360	2398.000	0.006

	Case	4.504	0.591	90.530	7242.000	4.540		
PWDD(cm)	Control	0.403	0.061	79.560	6365.000	0.410	3125.000	0.797
	Case	0.412	0.075	81.440	6515.000	0.400		
IVSS(cm)	Control	0.957	0.171	79.430	6354.500	0.950	3114.500	0.770
	Case	0.973	0.179	81.570	6525.500	0.950		
LVDS(cm)	Control	2.302	0.299	63.610	5088.500	2.340	1848.500	<0.001
	Case	3.740	4.999	97.390	7791.500	2.700		
PWDS(cm)	Control	0.402	0.060	76.080	6086.500	0.410	2846.500	0.225
	Case	0.578	0.725	84.920	6793.500	0.400		
EF(%)	Control	72.330	20.876	99.690	7975.500	79.000	1664.500	<0.001
	Case	60.660	27.283	61.310	4904.500	71.000		
FS(%)	Control	43.090	12.761	98.890	7911.000	47.000	1729.000	<0.001
	Case	35.000	16.236	62.110	4969.000	40.000		
LVM(gr)	Control	71.020	23.568	75.610	6049.000	69.630	2809.000	0.226
	Case	76.210	24.279	84.440	6671.000	72.290		
Simpson LVDD (ml)	Control	82.903	30.728	77.110	6168.500	88.350	2928.500	0.354
	Case	100.794	117.347	83.890	6711.500	81.800		
Simpson LVDS (ml)	Control	41.908	17.860	69.580	5566.500	44.700	2326.500	0.003
	Case	50.981	19.380	91.420	7313.500	50.700		
Simpson EF(%)	Control	49.510	9.798	92.930	7434.000	48.000	2206.000	0.001
	Case	42.530	10.521	68.080	5446.000	44.000		
MPI	Control	0.628	0.198	64.030	5122.500	0.593	1882.500	<0.001
	Case	0.757	0.205	96.970	7757.500	0.754		
Peak E/ peak A	Control	2.077	0.388	95.380	7630.000	2.130	2010.000	<0.001
	Case	1.819	0.476	65.630	5250.000	1.760		
LAd /AOd	Control	1.055	0.203	65.460	5237.000	1.000	1997.000	<0.001
	Case	1.199	0.206	95.540	7643.000	1.210		

Las/Aos	Control	0.727	0.161	60.850	4868.000	0.666	1628.000	<0.001
	Case	0.894	0.205	98.630	7693.000	0.863		
RWT	Control	0.189	0.024	86.010	6881.000	0.193	2759.000	0.132
	Case	0.185	0.038	74.990	5999.000	0.180		
LVMI(gr/m^2)	Control	26.304	8.729	75.980	6078.000	69.630	2838.000	0.217
	Case	28.229	8.935	85.030	6802.000	72.290		
DTI								
a (ms)	Control	328.01	75.64	57.85	4628.00	316.00	1388.00	<0.001
	Case	431.04	102.19	103.15	8252.00	461.00		
ICT(ms)	Control	86.94	16.36	53.81	4304.50	89.00	1064.50	<0.001
	Case	117.51	31.57	107.19	8575.50	117.00		
IRT(ms)	Control	70.49	11.31	54.41	4352.50	67.00	1112.50	<0.001
	Case	92.36	35.53	106.59	8527.50	89.00		
MPI(ms)	Control	0.50	0.08	41.13	3290.00	0.49	50.00	<0.001
	Case	0.90	0.21	119.88	9590.00	0.88		

Simpson EF : EF was calculated in the apical chamber, LVDD: left ventricular end-diastolic dimension, a: is the time of interval between the end and the start of trans-mitral and trans-tricuspid flow, At: Acceleration time, Dt: deceleration time, Peak E: early mitral and tricuspid valve flow velocity , PeakA: late mitral and tricuspid valve flow velocity, LAd: Diameter of LA in Diastole, Aod: Diameter of Aorta in Diastole, Las: Diameter of LA in Systole , Aos: Diameter of Aorta in Systole, Et: ejection Time (for Aorta and Pulmonary), PWDD : posterior wall dimension in diastole. IVSD: interventricular septal dimension in Diastole, IVSS: interventricular septal dimension in systole, EF: ejection fraction, FS: fractional shortening, LVM: left ventricular mass, RWT: relative wall thickness. MPI: myocardial performance index, LVMI: left ventricular mass index.

Table-4: case-control comparison of some conventional and Doppler tissue Echocardiographic Right Heart functions

Variables	Groups	Mean	Std. Deviation	Mean Rank	Sum of Ranks	Meadian	Mann-Whitney U	P-value
Conventional								
a (ms)	Control	433.8	35.553	65.36	5228.5	433	1988.5	<0.001
	Case	459.69	46.647	95.64	7651.5	456		
AT (ms)	Control	66.39	9.412	77.35	6188	67	2948	0.383
	Case	68.13	11.046	83.65	6692	67		
DT (ms)	Control	142.48	20.697	76.42	6113.5	144	2873.5	0.263
	Case	146.06	24.659	84.58	6766.5	150		
Peak E (cm/s)	Control	70.123	12.6691	90.53	7242	68.8	2398	0.006
	Case	62.275	20.5	70.48	5638	61.6		
Peak A (cm/s)	Control	48.076	12.392	73.74	5899	46.6	2659	0.065
	Case	49.131	16.5522	87.26	6981	48.7		
ET (ms)	Control	271.06	25.639	94.62	7569.5	267	2070.5	<0.001
	Case	255	23.425	66.38	5310.5	256		
MPI	Control	0.594	0.113	43.98	3518	0.603	278	<0.001
	Case	0.9284	0.20665	117.03	9362	0.9		
Peak E/ Peak A	Control	1.5104	0.30525	92.56	7405	1.385	2235	0.001
	Case	1.3322	0.36668	68.44	5475	1.263		
DTI								
MPI	Control	0.594	0.113	43.98	3518	0.603	278	<0.001
	Case	0.9284	0.20665	117.03	9362	0.901		
a (ms)	Control	276.9375	33.83143	63.54	5083	272	1843	<0.001
	Case	401.3875	121.57693	97.46	7797	461		
ICT (ms)	Control	73.35	12.261	63.43	5074.5	72	1834.5	<0.001
	Case	87.71	24.076	97.57	7805.5	83		
IRT (ms)	Control	89.71	20.868	50.05	4004	89	764	<0.001
	Case	132.41	40.909	110.95	8876	123		

a: is the time of interval between the end and the start of trans-mitral and trans-tricuspid flow, At: Acceleration time, Dt: deceleration time, Peak E: early mitral and tricuspid valve flow velocity , Peak A: late mitral and tricuspid valve flow velocity, Et: ejection Time (for Aorta and Pulmonary) MPI: myocardial performance index, ICT: isovolumic contraction time. IRT: isovolumic relaxation time.

Table-5: Patients' comparison of some conventional and Doppler tissue echocardiographic Heart functions

Variables	NT-ProBNP	N	Mean	SD	t-test	P- value
DT (ms)	<=100	50	146.7	28.622	-0.612	0.543
	>100	30	150.57	25.125		
Peak E (cm/s)	<=100	50	93.326	17.464	-1.359	0.178
	>100	30	99.117	19.9906		
Peak A (cm/s)	<=100	50	53.944	13.65	-0.807	0.422
	>100	30	56.84	18.2941		
AT (ms)	<=100	50	459.06	48.135	-0.154	0.878
	>100	30	460.73	44.843		
DT (ms)	<=100	50	144.78	24.423	-0.598	0.552
	>100	30	148.2	25.319		
IVSD (cm)	<=100	50	0.718	0.1265	-1.009	0.316
	>100	30	0.744	0.0854		
LVDD (cm)	<=100	50	4.398	0.627	-2.107	0.038
	>100	30	4.68	0.4854		
LVM (gr)	<=100	50	73.17	27.245	-1.474	0.144
	>100	29	81.46	17.261		
Simpson LVDS (ml)	<=100	50	47.012	18.3337	-2.435	0.017
	>100	30	57.597	19.563		
Peak E/ peak A	<=100	50	1.8017	0.44913	-0.427	0.671
	>100	30	1.8489	0.52372		
LAd/AOd	<=100	50	1.1891	0.1941	-0.563	0.575
	>100	30	1.216	0.22637		

LVMI (gr/m^2)	<=100	50	27.1003	10.09081	-1.469	0.146
	>100	30	30.1101	6.29086		

Simpson EF: EF was calculated in the apical chamber, LVDD: left ventricular end-diastolic dimension, a: is the time of interval between the end and the start of trans-mitral and trans-tricuspid flow, At: Acceleration time, Dt: deceleration time, Peak E: early mitral and tricuspid valve flow velocity, PeakA: late mitral and tricuspid valve flow velocity, LAd: Diameter of LA in Diastole, Aod: Diameter of Aorta in Diastole, Las: Diameter of LA in Systole , Aos: Diameter of Aorta in Systole, Et: ejection Time (for Aorta and Pulmonary), PWDD: posterior wall dimension in diastole. IVSD : interventricular septal dimension in Diastole, IVSS: interventricular septal dimension in systole, EF: ejection fraction, FS: fractional shortening, LVM: left ventricular mass, RWT: relative wall thickness, MPI: myocardial performance index, LVMI: left ventricular mass index, ICT: isovolumic contraction time. IRT: isovolumic relaxation time.

Table-6: Patients' comparison of some conventional and Doppler tissue echocardiographic Left heart functions

Variables	NT-ProBNP	Mean	Std. Deviation	Median	Mean Rank	Sum of Ranks	MW Value	P-value
Conventional								
a (ms)	<=100	439.94	34.954	439	40.98	2049	726	0.811
	>100	428.3	59.97	433	39.7	1191		
AT (ms)	<=100	60.98	7.558	61	39.65	1982.5	707.5	0.665
	>100	61.43	8.866	61	41.92	1257.5		
Aod (cm)	<=100	2.7526	2.81071	2.28	36.94	1847	572	0.077
	>100	4.8213	7.26998	2.505	46.43	1393		
Lad (cm)	<=100	3.3046	3.88382	2.755	35.29	1764.5	489.5	0.010
	>100	5.5783	8.17794	3.035	49.18	1475.5		
Aos (cm)	<=100	2.5304	2.39039	2.18	37.91	1819.5	643.5	0.432
	>100	4.307	6.44947	2.275	42.05	1261.5		
Las (cm)	<=100	2.254	2.7162	1.87	36.08	1732	556	0.092
	>100	3.896	5.9645	1.955	44.97	1349		
ET (ms)	<=100	248.84	22.204	250	40.04	2002	727	0.818
	>100	249.4	19.114	250	41.27	1238		

PWDD (cm)	<=100	0.4132	0.07604	0.4	40.81	2040.5	734.5	0.877
	>100	0.4107	0.07315	0.405	39.98	1199.5		
IVSS (cm)	<=100	0.9653	0.20167	0.94	38.67	1933.5	658.5	0.363
	>100	0.9853	0.13567	0.965	43.55	1306.5		
LVDS (cm)	<=100	2.9198	3.01788	2.475	34.7	1735	460	0.004
	>100	5.106	7.04156	2.845	50.17	1505		
PWDS (cm)	<=100	0.477	0.4426	0.4	39.28	1964	689	0.543
	>100	0.7467	1.02662	0.41	42.53	1276		
EF (%)	<=100	56.85	30.775	71	39.65	1982.5	707.5	0.672
	>100	67.02	18.993	71.5	41.92	1257.5		
FS (%)	<=100	32.86	18.214	40.5	39.45	1972.5	697.5	0.601
	>100	38.56	11.685	40.5	42.25	1267.5		
Simpson LVDD (ml)	<=100	101.544	147.4314	77.7	35.12	1756	481	0.008
	>100	99.543	27.9834	96.75	49.47	1484		
Simpson EF (%)	<=100	42.72	10.734	43.5	40.28	2014	739	0.913
	>100	42.2	10.327	43.5	40.87	1226		
MPI	<=100	0.7772	0.17081	0.7561	41.61	2080.5	694.5	0.581
	>100	0.7227	0.2524	0.7587	38.65	1159.5		
LAs/ Aos	<=100	0.8754	0.19651	0.861	38.18	1832.5	656.5	0.514
	>100	0.9236	0.21834	0.877	41.62	1248.5		
RWT	<=100	0.1898	0.03397	0.186	45.1	2255	520	0.022
	>100	0.178	0.04319	0.168	32.83	985		
DTI								
a (ms)	<=100	416.68	113.23777	456	38.06	1903	628	0.225
	>100	454.9667	76.36459	467	44.57	1337		
ICT (ms)	<=100	115.48	37.573	115	38.25	1912.5	637.5	0.262
	>100	120.9	17.604	119.5	44.25	1327.5		

IRT (ms)	<=100	94.96	42.945	89	41.17	2058.5	716.5	0.738
	>100	88.03	17.073	86	39.38	1181.5		
MPI	<=100	0.8814	0.24347	0.83	35.66	1783	508	0.016
	>100	0.9338	0.15009	0.924	48.57	1457		

Simpson EF : EF was calculated in the apical chamber, LVDD: left ventricular end-diastolic dimension, a: is the time of interval between the end and the start of trans-mitral and trans-tricuspid flow, At: Acceleration time, Dt: deceleration time, Peak E: early mitral and tricuspid valve flow velocity , PeakA: late mitral and tricuspid valve flow velocity, LAd: Diameter of LA in Diastole, Aod: Diameter of Aorta in Diastole, Las: Diameter of LA in Systole , Aos: Diameter of Aorta in Systole, Et: ejection Time (for Aorta and Pulmonary), PWDD: posterior wall dimension in diastole. IVSD : interventricular septal dimension in Diastole, IVSS: interventricular septal dimension in systole, EF: ejection fraction, FS: fractional shortening, LVM: left ventricular mass, RWT: relative wall thickness. MPI: myocardial performance index, LVMI: left ventricular mass index, ICT: isovolumic contraction time. IRT: isovolumic relaxation time.

Table-7: Patients' comparison of some conventional and Doppler tissue echocardiographic Right heart functions

Variables	NT-ProBNP	Mean	Std. Deviation	Median	Mean Rank	Sum of Ranks	MW Value	P-value
Conventional								
a (ms)	<=100	67.88	11.44	67	39.45	1972.5	697.5	0.597
	>100	68.53	10.533	69.5	42.25	1267.5		
Peak E (cm/s)	<=100	66.209	19.4371	68.25	44.43	2221.5	553.5	0.051
	>100	55.718	20.8637	60.2	33.95	1018.5		
Peak A (cm/s)	<=100	52.006	15.5919	48.7	43.38	2169	606	0.152
	>100	44.339	17.2501	48.3	35.7	1071		
ET (ms)	<=100	252.52	22.47	250	38.12	1906	631	0.234
	>100	259.13	24.768	256	44.47	1334		
MPI	<=100	0.8982	0.18657	0.8672	37.34	1867	592	0.116
	>100	0.9786	0.23094	0.9135	45.77	1373		
Peak E/Peak A	<=100	1.3583	0.41449	1.338	42.01	2100.5	674.5	0.453
	>100	1.2888	0.26995	1.261	37.98	1139.5		

DTI								
MPI	<=100	0.8982	0.18657	0.867	37.34	1867	592	0.116
	>100	0.9786	0.23094	0.914	45.77	1373		
A (ms)	<=100	385.5	128.2073	422.5	38.06	1903	628	0.225
	>100	427.8667	106.45081	469.5	44.57	1337		
ICT (ms)	<=100	85.44	19.223	83	38.57	1928.5	653.5	0.335
	>100	91.5	30.511	89	43.72	1311.5		
IRT (ms)	<=100	128.44	38.397	122.5	37.85	1892.5	617.5	0.186
	>100	139.03	44.67	128	44.92	1347.5		

a: is the time of interval between the end and the start of trans-mitral and trans-tricuspid flow, At: Acceleration time, Peak E: early mitral and tricuspid valve flow velocity , PeakA: late mitral and tricuspid valve flow velocity, LAd: Diameter of LA in Diastole, Aod: Diameter of Aorta in Diastole, Las: Diameter of LA in Systole , Aos: Diameter of Aorta in Systole, Et: ejection Time (for Aorta and Pulmonary), PWDD : posterior wall dimension in diastole. IVSD : interventricular septal dimension in Diastole, IVSS: interventricular septal dimension in systole, EF: ejection fraction, FS : fractional shortening, LVM: left ventricular mass, RWT: relative wall thickness. MPI: myocardial performance index, **LVMI:** left ventricular mass index, ICT: isovolumic contraction time. IRT: isovolumic relaxation time.