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# Early identification of heart failure in patients with thalassemia major by NT-pro-BNP examination. Correlation with echocardiographic parameters of morphology and function

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**Abstract**
**Aims:** To identify early heart failure in patients with thalassemia major by examining NT-pro-BNP and to correlate echocardiographic parameters.
**Materials and methods:** We evaluated 37 consecutive patients with homozygous β-thalassemia and 50 age-matched healthy controls by NT-pro-BNP levels and echocardiography.
**Results:** NT-proBNP levels were significantly higher in TM cohort compared to healthy controls 169.3±166.3 versus 33±19.5 pg/ml. ($p<0.001$). There were 11 (29.7%) patients with elevated NT-pro-BNP. Ultrasound and MRI LAVi (ml/m²) were significantly enlarged with borderline depression of left atrial emptying fraction. TM NT-proBNP+) had significantly larger left atrial volume index LAVi ($p=0.025$) compared to TM NT-proBNP-, but all other indices were no different. There was a moderate yet significant correlation between NT-pro-BNP and LAVi – $r=0.44$, $p=0.009$ and between LVMMi and LAVi- $r = 0.480$, $p= 0.004$.
**Conclusions:** The only significant difference between the two TM groups - NT-proBNP positive and NT-proBNP negative was left atrial volume index LAVi.

**Keywords:** heart failure, beta-thalassemia, echocardiography, MRI, NT-pro BNP, left atrium

## Introduction
Cardiac involvement remains the leading cause of morbidity and mortality among patients with transfusion-dependent Thalassemia Major (TM) [1, 2, 3, 4]. Myocardial iron deposition together with increased cardiac output are considered the principal causes of heart failure, although patients are regularly transfused and are on optimal chelation regimen [5, 6, 7, 8, 9]. The aim of the present study was to diagnose early heart failure in thalassemia major by examining NT-pro BNP and to look for corresponding signs of cardiac dysfunction by both echocardiography and/or cardiac magnetic resonance imaging.

## Materials and Patients
We evaluated 37 patients (mean age 32±11) with homozygous β-thalassemia attending the Center of Rare Diseases at our institution. All patients were regularly transfused at three to five week time intervals in order to maintain hemoglobin level of 90-100 g/l and were on standard chelation regimens. Patients with abnormal renal function (GFR<80 ml/m$^2$/min, systolic blood pressure ≥140 mm Hg, abnormal blood sugar levels or manifest thyroid dysfunction or in atrial fibrillation were excluded from the study. Fifty apparently healthy subjects (mean age 31±8.5) with no clinical, electrocardiographic, echocardiographic or NT-pro BNP evidence of cardiovascular diseases were compared to TM patients.
For the quantitative measurement of NT pro-BNP heparinized plasma was used and analyzed on IMMULITE 2000 automatic imunoanalyser. The test is a solid-phase, two-site chemi luminescent immune metric assay, with an analytical sensitivity of 10 pg/ml and reportable range of 20-35000 pg/ml. The assay is traceable to an internal standard manufactured by SIEMENS and results should be interpreted using the reference ranges of the method. The most appropriate cut-off thresholds are considered 125 pg/ml for patients younger than 75 years and 450 pg/ml for patients 75 years or older [12].
Echocardiograms were performed with a commercially available Aloka Prosound α7 machine. All patients were examined in the left lateral decubitus position using multi-frequency 2.5–5 MHz phased-array transducer. The heart was scanned from all standard views and three cardiac cycle loops from 4-chamber apical were stored for TDI strain and strain rate measurements offline. All M-mode and Doppler measurements were performed according to guidelines [10]. Chamber dimensions were corrected for body surface area (BSA). Left ventricular volumes with left ventricular ejection fraction (LVEF) and left atrial volumes at end-systole (LAV

max) and at end-diastole (LAV min) were measured from 4-chamber apical view using the Simpson rule. Transmitral inflow Doppler velocities were measured by placing the sample volume at the tips of the mitral leaflets. Tissue-Doppler velocity measurements were performed as the sample volume was placed at the basal interventricular septum with the ultrasound beam parallel to the interventricular septum and at the lateral wall. The ratio E/Em (E Doppler mitral fast inflow to the corresponding tissue Doppler Em) was calculated and the mean value of the septal and lateral wall of the LV was taken as an index of left ventricular diastolic function [11].

Studies of Cardiac Magnetic Resonance Imaging were conducted with a Siemens MR using a 5-channel cardiac coil. Values of T2* above 20 secs were considered normal and below 10 secs were considered abnormal with heavy iron burdening. In 30 patients measurement of left ventricular end-systolic and end-diastolic volumes was made using syngoMR Cardiac 4D off-line "long axis and short axis" platform and EF was calculated. LVMM was calculated in the same calculation process contouring endo and epicardial borders. Left atrial volumes were measured using biplane method formula with maximal and minimal left atrial volumes used for left atrial emptying fraction calculation [12].

**Statistical Analysis**

The Hospital Ethics committee and all patients approved the protocol and controls gave written informed consent. Data are presented as mean ± SD for continuous variables and numbers as percentage for categorical data. Normality was assessed by Kolmogorov-Smirnov test. In case of diversion from normal distribution, as with NT-pro-BNP, the central tendency was presented as median (interquartile range). Log transformation of data for NT-proBNP to account for the skewed distribution was performed as well. Statistically significant differences between groups of continuous variables were determined by using unpaired Student's t-test or in case of abnormal distribution- Mann-Whitney U-test was used. Correlations of NT-pro-BNP values and LA and LV parameters were estimated using Pearson's r or Spearman's rank correlation tests, whenever appropriate. A value of $p < 0.05$ was considered statistically significant. All statistical tests were carried out with the commercially available SPSS v.23 (SPSS, Texas, USA) software package.

**Results**

Overall, 87 participants were included – 37 in the TM group and 50 healthy individuals serving as controls. TM patients were slightly older – 32.3±10.9 vs 31.1±8.5 years (p=0.55) and more than half of them were females – 54% vs 50% (p=0.71).

NT-proBNP (pg/ml) were significantly higher in the TM cohort 169.3±166.3 (20-724) compared to healthy controls-33±19.5 (20-55) pg/ml. (p<0.001). (Fig 1). Eleven patients (29.7%) had NT-pro-BNP elevated above the upper normal limit of >125 pg/ml fulfilling criteria for diagnosis of heart failure according to the ESC Guidelines [10]. NT-proBNP levels of TM patients with normal values were higher compared to controls as well (p<0.01; 59.5±32 vs 33±19.5 pg/ml).

The comparison of the examined demographic, laboratory and imaging variables between the two groups is presented on Table 1. Patients with TM had significantly smaller BSA and significantly higher mean heart rate (beats/min), LVEDDi (mm/m2), LVESVi (mm/m2), SV (ml), CO (l/min) and CI (l/min/m²). At the same time LVMMi (g/m2) and RWT were also increased compared to controls. Left ventricular EF was however, normal, though systolic myocardial velocities -Sm (cm/s) and deformations indices - strain and strain rate (1/sec) were significantly lower. Transmitral flow in this study showed increase in velocities of both early and late diastolic filling the latter significantly so. Transmitral E/A velocities ratio was reduced and E/Em was not different compared to controls. Left atrial indices showed enlarged LAVi (ml/m²) and depression of LAEF, which also was significant. (p<0.05)

TM patients with elevated NT-proBNP (TM NT-proBNP+) and TM patients with normal NT-proBNP (TM NT-proBNP-) were then compared and results presented in Table 2. The only significant difference between the two groups was left atrial volume index LAVi (P=0,025) and all other indices examined were not statistically different. (Fig 2).

There was a moderate correlation between NT-pro-BNP and LAVi – (r=0.44, p=0.009) (Fig. 3). There was also moderate correlation between LVMMi and LAVi- (r = 0.480, p= 0.004) and poor correlation of NT-pro-BNP and LVMMi (r = 0.265, p= 0.143). The values of T2* between the two TM groups in our study: with normal NT-proBNP - 24±14 secs and elevated NT-pro BNP -28±9 secs were not significantly different - p=0.38. There was no significant correlation between NT-proBNP and T2* values. (Fig.4). There was 40% sensitivity for T2* values and 63.6 % sensitivity and 88.4% specificity for LAVi for detection or rejection of heart failure based on NT-proBNP values.

**Discussion**

As an adaptive mechanism of chronic anemia, heart rate is expected to be higher in TM patients. Some authors also found a higher heart rate in patients with TM compared to controls [16, 37], but others did not [17, 34]. We have not detected differences in systolic or diastolic arterial pressures compared to healthy subjects. Other authors also found no difference in blood pressure between groups [23, 34]. Some however found significant reduction in systolic, diastolic and mean BP values in thalassemia compared to controls [16, 37].

The lower BSA in patients with TM is the result of impaired physical development due to chronic anemia. Lower BSA values were reported by a number of authors [16, 17, 34] Increased left ventricular volumes indexed to BSA were found in the TM group. There was no difference between control and study groups however if we compared volumes not indexed to body surface area. The results obtained by other authors also indicate increased volumes of the TM group than in the control group [16, 17, 30, 37]. Increased indexed end-diastolic and end-systolic dimensions of the left ventricle for this study - were similar and close to other researchers- Kostapoulou (37) and in agreement with several other studies [16, 17, 34]. Stroke volume, cardiac output and cardiac index were also increased in patients with TM compared to the control group. In their follow-up, Bossi *et al* [16] and others [17] also found significant difference between stroke volume and cardiac index when

comparing thalassemia cohorts to controls. Both increase transmitral velocities and cardiac output are a sign of the hypercirculatory high output state in these patients.Left ventricular mass index was significantly higher in the TM group compared to healthy subjects in several studies [16, 33]. LVMMi obtained by Bossi *et al* [16] are 99.2± 22.1 g/m² for the TM group and 79.1±11.6 g/m² for the control group. (p <0.0001) The values obtained by Bigle *et al* (33) are higher- 139±42 for TM patients and 92±12 g/m² for controls (p <0.001). The TM patients had also increased relative wall thickness. Increased LVMMi and RWT reflect left ventricular remodeling found also by Bossi *et al*. [16] and Garadah *et al*. [31]. Whether increased left ventricular mass results from iron accumulation or other mechanisms is still debatable. Stoyanova *et al* [14] demonstrated increased fibrosis and myocardial muscle mass in non-transfused thalassemia mice model. A decade earlier, Georgieva *et al* [15] proved that severity of iron-deficiency anemia correlates with left ventricular size and mass with complete or partial reversal after correction of anemia. Although etiology in thalassemia and iron deficiency anemias is different, apparently there are common pathways and adaptive mechanisms induced by hypoxic conditions which lead to similar structural changes of the left ventricle. There was no significant difference between the LVEF of the examined groups- 60±7,4% for TM patients vs 62±5,9% for healthy subjects (p=0,158) and values were similar in most studies [16, 17, 30, 33].

Systolic myocardial tissue Doppler velocities at the mitral annulus were decreased and with borderline significance between the thalassemia and the control group as was found by others too [30, 31, 34]. However, the strain and the strain rate as measures of LV deformation were significantly reduced in the TM group, although being still within normal range. Hamdy *et al*. [32] and Bilge *et al* [33] have investigated the role of strain in patients with TM and both studies concluded that strain imaging can be helpful in precise assessment of myocardial function and can be used for early detection of impairment of systolic or diastolic myocardial performance.

The size of the left atrium, measured as an indexed left atrial volume was significantly different in TM patients and in the control group (29 ± 7 ml/m² vs 19 ± 7ml/m² ; p <0.0001). The indexed left atrial volume correlated with of log transformed NT-proBNP value. (r =0.44, p=0.009, fig.3). Indexed left atrial volumes was also significantly enlarged in TM patients with elevated NT-proBNP values 35 ± 7ml/m² vs 26 ± 7ml/m² in the group of TM patients with normal NT-proBNP values. (p <0.025). In cardiac MRI examination indexed left atrial volumes expectedly were found to be greater 34.4±9.1 ml/m² compared to echocardiography 29±7 ml/m² and significantly different between TM NT-proBNP + and NT-pro BNP- patients when examined (40.6±10.3 vs 27±5.3; p=0.076*) Left atrial emptying fraction was lower -39±12 percentage for TM group vs 45±9% for controls. (p=0.05) Left-atrial contraction was investigated previously [35, 37, 39] and both active and passive emptying fractions were decrease in patients with TM. Kostopoulou *et al* [37] demonstrated early deterioration of active and passive atrial contraction and correlated inversely with atrial natriuretic peptides. Reduced left atrial active emptying fraction in beta-thalassemia patients was confirmed by real-time three-dimensional echocardiography by Ageli *et al* [35] and this was the only echocardiographic parameter that was statistically different. There was no difference between the volumes of the two groups in this study: 35.5 ± 13.4ml vs 31.8 ± 9.8ml, but they were not indexed to BSA. Mahmoud S. Wehbe *et al*. [38] examined left atrial active contractile function by MRI in 38 patients with systemic iron overload and concluded that active atrial emptying fraction parameters are significantly decreased. There are now multiple publications on left atrial volumes and function in correlations with NT-pro BNP in various disease states- in patients on chronic dialysis [41], in patients with heart failure with preserved ejection fraction [42], non-ischemic cardiomyopathy with poor ejection fraction [43], in post-mitral valvuloplasty of mitral stenosis [44] and in severely depressed systolic function [45] indicating that atrial stretch and pressure are also important determinant of natriuretic elevations [38]. It was even shown that minimal left atrial volume was more closely correlated with natriuretic peptides than the maximal one [40]. The rise of NT-proBNP has been systemically studied in patients with TM and has been associated with diastolic dysfunction in thalassemia patients. [17, 18, 19, 20] or was considered an early index of myocardial siderosis detected by MRI [47]. The ratio of E/Em as an important marker of diastolic dysfunction was either normal or increased especially in cases of restrictive pattern of diastolic dysfunction and correlated with NT-proBNP. Kremastinos *et al*. [17] found that NT-proBNP was in correlation with E/Em in 52 TM patients with LVEF >50% and concluded that NT-proBNP may be an early marker of diastolic dysfunction. Similarly Garadah *et al* [31] in a follow-up of 38 TM patients reported higher NT-proBNP, greater E-wave velocity with shorter deceleration time and a greater E/A ratio with a tendency to restrictive diastolic disfunction. They establish a higher E/Em ratio and lower Sm and Em values compared to controls. Other authors have also found restrictive type or other signs of impaired diastolic filling [21, 22, 23, 24, 25, 26]. In 2016 however, Bezhad Alizadeh *et al* [20] examined 50 patients with TM with preserved ejection fraction and found no correlation with E/Em values. In follow - up of 34 TM patients Akpinar (30) stated that cardiac volumes were found to be increase significantly, but ejection fraction and diastolic function were normal in both groups. NT-proBNP was higher in the TM group and correlated with systolic longitudinal myocardial velocities. Standard echo-Doppler indices of diastolic function correlate not so well with LV diastolic pressure transients. The diagnosis of diastolic heart failure cannot be made on the basis of a single echo-Doppler parameter but, rather, all parameters must be examined in concert and used in combination [48].

In this study, we compared two subgroups of patients with thalassemia major - with elevated NT-pro-BNP and with normal NT-pro-BNP and found that the only parameter that was significantly changed was indexed left atrial volume measured by both two-dimensional echocardiography and cardiac magnetic resonance imaging. These changes in left atrial dimensions with elevated wall stress may explain the increased levels in NT-pro-BNP and may have important prognostic implications, as increased LA volumes are a major determinant of unfavorable outcome in patients with HF [49, 50].

## Conclusions

It is very well known from a clinical standpoint how difficult it is to distinguish symptoms of easy fatigability and effort dyspnea in patients with chronic anemia, heart failure or both as is the case in TM patients. Due to anemia and iron deposition patients with TM have compensatory hemodynamic, structural and functional cardiac changes. Since all indices were significantly different from healthy subjects but within normal range or borderline, regular echocardiographic follow-up of TM patients with NT-pro-BNP determination is clinically beneficial for early detection of deterioration of cardiac function. Application of strain is an important method for detecting LV systolic dysfunction but only left atrial volume index in this study discriminated patients with TM with elevated NT-pro-BNP from those with normal ones and correlated well with NT-pro BNP levels.

**Table 1:** Major parameters in the TM and the control group.

| | **TM patients N=37** | **Healthy Controls N=50** | |
|---|---|---|---|
| Age | 32.4±10,9 | 31±8.5 | p=0.55 |
| BSA ($m^2$) | 1.66±0,2 | 1.80±0,25 | P=0.007 |
| SBP (mm Hg) | 109 ± 14 | 113±10 | P=0.352 |
| DBP (mm Hg) | 69 ± 7 | 72±10 | P=0.505 |
| Heart Rate (beats/min) | 83±11 | 75 ±12 | P=0.017 |
| NT-proBNP (pg/ml) | 169.3±166.3 | 33±19.5 | P<0.0001 |
| LVEDDi ($mm/m^2$) | 30.55±4,59 | 25.31±2,90 | P<0.0001 |
| LVESVi ($mm/m^2$) | 19.31±3.95 | 16.52±2.47 | P=0.001 |
| RWT | 0.47±0,12 | 0.41±0.06 | P=0.037 |
| LVMMi (g/m2) | 122±31 | 79±19 | P=0.0001 |
| EDV (ml/m2) | 62±15 | 48±9 | P<0.0001 |
| MRI EDV (ml/m2) | 84±24 | | R= 0.78 |
| ESV (ml/m2) | 24±8 | 19±5 | P=0.001 |
| MRI ESV (ml/m2) | 31±11 | | R= 0.82 |
| SV (ml) | 61.81±21.02 | 53.39±13.34 | P=0.045 |
| CO (l/min) | 5.14±2,06 | 4.04±1.28 | P=0.008 |
| CI ($l/min/m^2$) | 3.07±0.91 | 2.21±0.6 | P<0.0001 |
| LVEF (%) | 60±7.4 | 62±5.9 | P=0.158 |
| MRI LVEF (%) | 63±5.2 | | R=0.5 |
| LAVi ($ml/m^2$) | 29±7 | 19±7 | P<0.0001 |
| MRI LAVi ($ml/m^2$) | 34.4±9.1 | | R=0.5 |
| LAEF (%) | 39±12 | 45±9 | P=0.05 |
| MRI LAEF (%) | 38.4±11.6 | | R=0.3 |
| E/A | 1.3±0.4 | 1.6±0.5 | P=0.047 |
| E (m/s) | 0.87±0.03 | 0.83±0,02 | P=0.27 |
| A (m/s) | 0.65±0,03 | 0.54±0.02 | P<0.001 |
| DT (msec) | 235±40 | 208±60 | P=0.35 |
| Em/Am | 1.45±0.16 | 1.62±0.23 | P=0.08 |
| Em (cm/s) | 16.2±4,3 | 18,7±3,5 | P=0,014 |
| Am (cm/s) | 11.1±2,7 | 11.4±2.4 | P=0,62 |
| E/Em | 5.5±1.6 | 5.2±1.6 | P=0.35 |
| Sm (cm/s) | 10.5±1.5 | 11.3±1.7 | P=0.055 |
| Strain | 32±9 | 37±9 | P=0.031 |
| Strain rate (1/sec) | 1.82±0.76 | 2.43±0.86 | P=0.004 |

BSA-body surface area; NT-proBNP- NT-pro Brain Natriuretic Peptide, SBP-systolic blood pressure, LVEDDi-left ventricular end-diastolic diameter indexed; LVESDi-left ventricular end-systolic diameter indexed; RWT-relative wall thickness; LVMMi- left ventricular muscle mass indexed; SV-stroke volume; CO- cardiac output; CI- cardiac index; LVEF-left ventricular ejection fraction; LAVi- left atrial volume indexed; LAEF- left atrial ejection fraction, DT-deceleration time, Sm-systolic myocardial velocity, Em-early diastolic filling myocardial velocity, E-early diastolic filling blood velocity, A-late diastolic filling blood velocity, Am-late diastolic filling myocardial velocity.

**Table 2:** Major echocardiographic parameters according to the level of NT-pro-BNP >125 pg/ml or less

| | **TM NT-proBNP-** | **TM NT-proBNP+** | **P value** |
|---|---|---|---|
| Age | 29.9±11 | 38± 8 | P=0.056 |
| Heart Rate | 83±11 | 77± 16 | P=0.194 |
| SBP (mm Hg) | 110 ± 14 | 114±10 | P=0.45 |
| DBP (mm Hg) | 70 ± 7 | 72±10 | P=0.55 |
| NT-proBNP (pg/ml) | 59.5±32 | 327±197 | P<0.0001 |
| T2* | 24±14 | 28±9 | P=0.38 |

| | | | |
|---|---|---|---|
| EDD | 49±7 | 52± 5 | P=0.347 |
| RWT | 0.47±0.12 | 0.45± 0.08 | P=0.726 |
| LVMMi | 122±31 | 144± 54 | P=0.141 |
| EDV ml/m2 | 60±14 | 66±17 | P=0.071 |
| MRI EDV ml/m2 | 81±25 | 82±20 | P=0.193 |
| ESV ml/m2 | 23±7 | 26±9 | P=0.341 |
| MRI ESV ml/m2 | 31±10 | 32±13 | P=0.146 |
| LAVi | 26.4±7 | 35.6± 16 | P=0.025* |
| MRI LAVi | 27±5.3 | 40.6±10.3 | P=0.076* |
| EF% | 60±7.4 | 60± 7.3 | P=0.945 |
| MRI EF% | 63.2± 6 | 62.9±7.2 | P=0.349 |
| LAEF% | 39±11 | 41±9 | P=0.674 |
| MRI LAEF% | 39.4±9.2 | 39.8±12.4 | P=0.46 |
| E m/s | 0.88±0.21 | 0.83±0.14 | P=0.58 |
| A m/s | 0.77±0.11 | 0.56±0.24 | P=0.023 |
| E/A | 1.2±0.4 | 1.2±0.6 | P=0.92 |
| DecT (msec) | 233±50 | 243±83 | P=0.67 |
| Sm(cm/s) | 10.1±1 | 10.2± 1 | P=0.551 |
| Em (cm/s) | 16.6±4.9 | 15.4±3.4 | P=0,44 |
| Am (cm/s) | 11.4±2.1 | 11.1±3.6 | P=0.80 |
| E/Em | 5.4±1.8 | 5.4±1.2 | P=0.93 |
| Em/Am | 1.5±0.2 | 1.6±0.2 | P=0.08 |
| Strain | 32±9 | 33± 7 | P=0.861 |
| Strain rate | 1.88±0.82 | 1.78±0.60 | P=0.34 |

BSA-body surface area; NT-proBNP- NT-pro Brain Natriuretic Peptide, SBP-systolic blood pressure, LVEDDi-left ventricular end-diastolic diameter indexed; LVESDi-left ventricular end-systolic diameter indexed; RWT-relative wall thickness; LVMMi- left ventricular muscle mass indexed; SV-stroke volume; CO- cardiac output; CI- cardiac index; LVEF-left ventricular ejection fraction; LAVi- left atrial volume indexed; LAEF- left atrial ejection fraction, DT-deceleration time, Sm-systolic myocardial velocity, Em-early diastolic filling myocardial velocity, E-early diastolic filling blood velocity, A-late diastolic filling blood velocity, Am-late diastolic filling myocardial velocity.

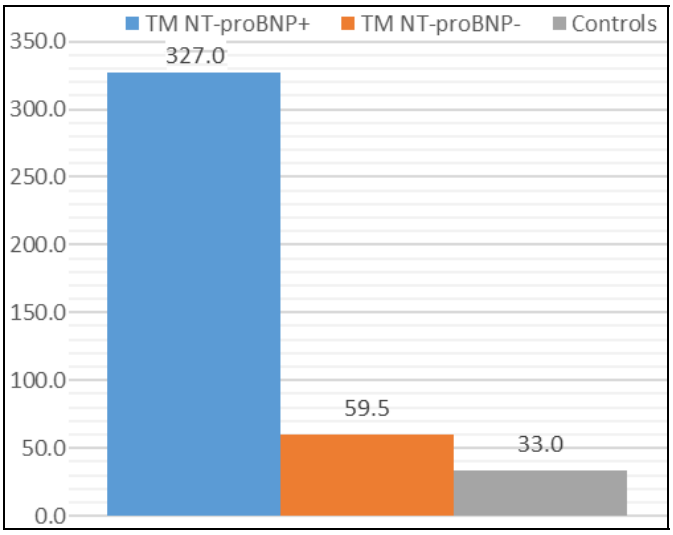


**Fig 1:** NT pro-BNP in patients with thalassemia major- TM NT-proBNP(+) - 327.0 pg/ml, TM N-proBNP(-) -59.5 pg/ml (p=0.001) and controls.

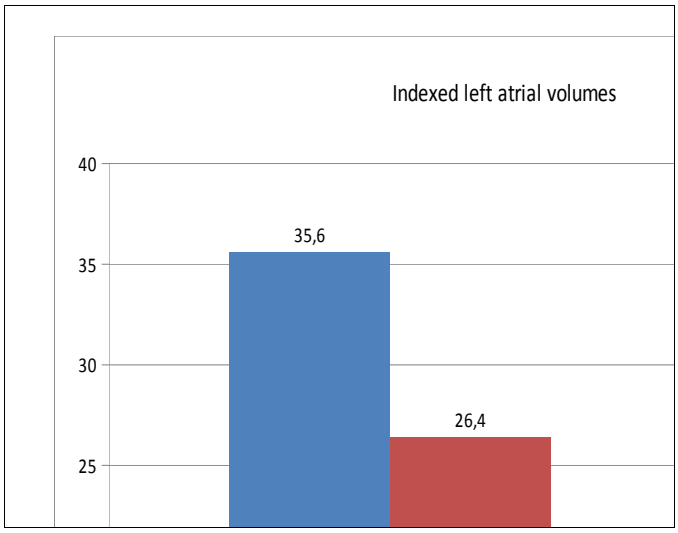


**Fig 2:** Indexed left atrial volumes in patients with thalassemia major NT–pro BNP (+) (blue)-35.6 ml/m2 and NT-proBNP(-) (red)-26.4 ml/m2 (p=0.025).

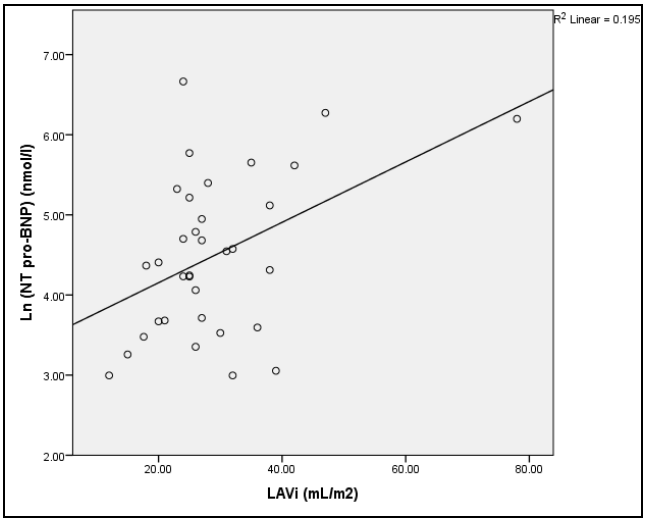


**Fig 3:** Correlation between LAVi and log transformed NT-proBNP in patients with thalassemia major, (r=0.44, p=0.009)

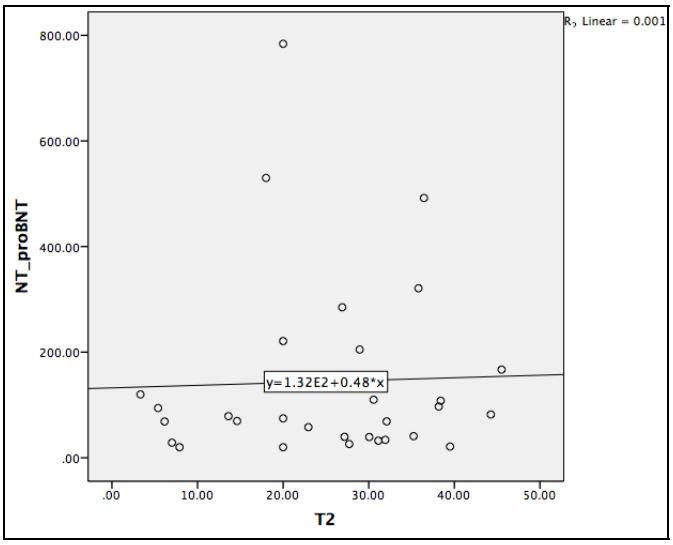


**Fig 4:** Correlation between T2* and log transformed NT-proBNP in patients with thalassemia major, r = 0,032, p= 0,0863.

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