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The value of N-terminal Pro-brain natriuretic peptide in pediatric pulmonary hypertension: A single center study

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Abstract

In the last decade, new pharmacological therapies have been developed that improve hemodynamics, exercise capacity and survival in patients with pulmonary hypertension. Subsequently, it has become of growing importance to accurately assess the severity and prognosis of the disease and the effectiveness of therapy in individual patients with pulmonary hypertension. The aim of the work is to assess the value of the N terminal pro-BNP in the diagnosis and prognosis of pediatric pulmonary hypertension. Our study is a prospective observational cohort study that was conducted on all patients (fulfilling the inclusion criteria) who were presented with pulmonary hypertension at the pediatric cardiology department of Cairo University Children's Hospital during the duration of the study (from January 2020 to September 2022). All patients were subjected to full medical history, general and cardiac examination, assessment of the WHO functional class, N-terminal pro-BNP, 6MWT and echocardiography during the initial assessment and the follow up. The total number of patients included in the study was 106. 30 patients (28.3%) were idiopathic, 27 patients (25.5%) were secondary to CHD, 35 patients (33%) were due to restrictive lung disease, and 13.2% due to other causes. Dyspnea was the most common presenting symptom. The NT pro-BNP level was significantly increased, with a median level of 851.5 with an IQR ranging from 220 to 5140.1 pg/ml. In our study, there was a significant positive correlation between the NT pro-BNP and the z score of the right ventricular end-diastolic diameter and the z score of the right atrial area. We had 22 mortality cases (19.6%) and 15 morbidity cases (13.4%). Pulmonary hypertension is a disabling disease affecting patients' quality of life and having a major impact on their mortality. Early diagnosis and administration of pulmonary vasodilators, as well as monitoring the progression of the disease and response to the medications, are critical. The NT pro-BNP is considered, besides its diagnostic importance, a useful prognostic indicator, especially when combined with other prognostic indicators.

Keywords: Pulmonary hypertension, Pro-BNP, 6MWD, Echocardiography, Mortality.

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1. Introduction

A Pulmonary arterial hypertension is defined as a mean pulmonary arterial pressure greater than 25 mmHg at rest, with a pulmonary artery wedge pressure less than 15 mmHg and an increased pulmonary vascular resistance greater than 3 Wood units×M2 [1]. Pulmonary hypertension may be idiopathic. However, secondary pulmonary hypertension may occur in many other types of diseases. This includes types of congenital heart disease, severe forms of lung disease, connective tissue diseases, or sickle cell disease [2]. In the last decade, new pharmacological therapies have been developed that improve hemodynamics, exercise capacity, and survival in patients with pulmonary hypertension. As a result, it has become of growing importance to accurately assess the severity and prognosis of the disease as well as the efficacy of therapy in an individual patient with pulmonary hypertension [3].

Several correlates of disease severity and survival have been described in adults with pulmonary hypertension. Hemodynamic and functional capacity parameters are currently the cornerstones in characterizing disease progression. Invasively obtainable hemodynamic parameters have been shown to represent disease severity and predict survival. Noninvasive parameters for functional capacity are used for the assessment of clinical condition, the severity of disease, and the effectiveness of therapy [4]. Six-minute walking distance (6MWD) has been shown to correlate well with World Health Organization (WHO) functional class and also with hemodynamic parameters. But in pediatric patients with pulmonary hypertension, the use of these parameters has specific drawbacks. In the pediatric age group, however, cardiac catheterization is mostly performed under general anesthesia, making repetitive catheterizations for follow-up unattractive. Exercise capacity tests as the

6MWD or maximal exercise tests are often not feasible and less validated in young children. Therefore, additional parameters to monitor disease severity, prognosis, and efficacy of treatment are highly needed in pediatric patients with pulmonary hypertension [5].

In pulmonary hypertension, the neurohumoral axis is activated, as evidenced by elevated circulating levels of brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP) and other neurohumoral markers as the Pressure overload of the right heart activates the natriuretic peptide system. Brain-type natriuretic peptide (BNP) is released in response to myocardial stretch from cardiomyocytes, where it has been synthesized as an inactive precursor (proBNP) and split into the active hormone BNP and the inactive N-terminal fragment (NT-proBNP). While BNP has a short half-life, NT-proBNP is not further metabolized and is eliminated only by renal excretion, resulting in a longer half-life. Therefore, NT-proBNP is preferably used in clinical routine as an indicator of myocardial dysfunction [6].

Our aim of the study was to evaluate the N-terminal Pro-BNP test as a simple non-invasive test in this high-risk type of patient, to assess the severity, prognosis, and outcome of the disease, and to compare the N-terminal Pro-BNP test with the other prognostic indicators.

2. Patients and Methods

This is a prospective observational cohort study that was conducted on all patients (fulfilling the inclusion criteria) who were presented with pulmonary hypertension at the pediatric cardiology department of Cairo University Children's Hospital during the duration of the study (from January 2020 to September 2022).

2.1 Inclusion criteria

1- Age: 3 Months to 18 Years.
2- Both genders are involved.
3- All patients with pulmonary hypertension were included except patients with pulmonary hypertension secondary to left-sided heart lesions (group 2) and patients with pulmonary hypertension due to operable shunt lesions.
4- Incident cases: newly diagnosed cases.
5- Prevalent cases: referred cases for management.

2.2 Exclusion criteria

1- Patients with persistent pulmonary hypertension of the newborn.
2- Patients with Pulmonary hypertension due to operable shunts.
3- Patients with pulmonary hypertension secondary to left sided heart lesions (group 2).

All patients were subjected to the following:

1- Complete history taking .
2- Clinical examination with special emphasis on:

- Wight and height and the corresponding percentiles.
- Vital signs including; heart rate, blood pressure and respiratory rate.
- The oxygen saturation.
- Neck veins examinations (congested or not).
- Signs of right-sided heart failure as Hepatomegaly, bilateral lower limb edema, or ascites.
- Clubbing as a sign of chronic hypoxia.
- Cardiac examination for signs of RV dilatation, palpable S2 and accentuated pulmonary component of S2.
- Chest examination for signs suggestive of respiratory cause such as, fine inspiratory crepitations in cases with ILD.

3- Chest X-ray.
4- High resolution CT chest was done in all cases.
5- Echocardiography for

- Assessment of CHD as in cases with Pulmonary hypertension secondary to shunt lesions.
- Assessment of Pulmonary Artery Pressure by :
  - TR velocity and PG:
  - PR velocity and PG:
  - PG across the shunt lesions if present.
  - Right ventricular end diastolic diameter and the z score of the RVEDD and RV/LV ratio to assess right ventricular dilatation.
  - Right atrial area to assess right atrial dilatation:
  - MPA diameter.
  - The tricuspid annular plane systolic excurtion (TAPSE) to assess right ventricular systolic function:
  - RVOT acceleration time:
- Signs of RV failure as :
  - Pericardial effusion.
  - Congested IVC with poor collapsibility

6- Six minute walk test (6MWT)

It is a submaximal exercise test that entails the measurement of distance walked over a span of 6 minutes. In this test, the patient rested for at least 10 min before 6MWT. Heart rate, blood pressure, and oxygen saturation (SO2) were measured, and levels of tiredness and dyspnea were determined both before and after the test and the 6MWD was determined.

7- N-terminal Pro-B NP test:

This assay employs the quantitative sandwich enzyme immunoassay technique (ELISA). An antibody specific for NT pro-BNP has been pre-coated onto a microplate. Standards and samples were pipetted into the wells and any NT-pro-BNP present was bound by the immobilized antibody. After removing any unbound substances, a biotin-conjugated antibody specific for NT pro-BNP was added to the wells. After washing, avidin conjugated Horseradish Peroxidase (HRP) was added to the wells. Following a wash to remove any unbound avidin-enzyme reagent, a substrate solution was added to the wells and color developed in proportion to the amount of NT-pro-BNP bound in the initial step. The color development was stopped and the intensity of the color was measured.

8-Cardiac Catheterization if not contraindicated:

- To assess the systolic, diastolic and the mean RV and pulmonary artery pressures.
- To assess Qp/Qs in cases with shunt lesions.
- To assess the PVR indexed to the body surface area.
- To assess Rp/Rs.
- Acute vasoreactivity was tested by hyperoxia test or prostacyclin analogues.
- To exclude other causes of pulmonary hypertension.

9- Multi-Slice CT heart and great vessels.
10- Thrombophilia panel was performed on the patients who were suspected of being thrombophilic.

11- Immune profile in patients who were suspected to have a collagen vascular disorder.
12- Metabolic screening in patients who were suspected to have an inborn error of metabolism.

The patients were followed and managed in the Pediatric Cardiology division in Cairo University's Specialized Pediatric Hospital, receiving the standard management as follows;

- Targeted pulmonary vasodilating agents:
  - Sildenafil from 0.5-1mg/kg/dose.
  - Endothelin receptor antagonists such as Bosentan (started with 1 mg/kg every 12 hours and then titrated to 2 mg/kg every 12 hours) and ambrisentan in selected cases.
  - Selexipag was added in selected cases.
- Antifailure measures as; frusemide and spironolactone.
- Digoxin in some cases.
- Treatment of the cause: as steroids in cases with pulmonary hypertension secondary to collagen vascular disease or cases with ILD.

The assessment was repeated after 3-6 months, except for cardiac catheterization.

During the follow up:

1- History taking and a complete physical examination was done with special emphasize on:
- WHO functional class.
- Improvement or worsening of the symptoms or appearance of a new symptom.
- Measurement of vital signs and oxygen saturation.
- General examination for signs of right-sided heart failure.
- Cardiac examination for signs of RV dilatation or muffled heart sounds in cases presented with pericardial effusion.

2- Follow up 6MWT.
3- Follow up echocardiography.
4- Follow up NT pro-BNP test.
5- Liver function tests were performed on a regular basis in all patients receiving bosentan therapy every 3 months.

2.3 Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

The used tests were :

I. Chi-square test: For categorical variables, to compare between different groups.
II. Monte Carlo correction: Correction for chi-square when more than 20% of the cells have expected count less than 5.
III. F-test (ANOVA): For normally distributed quantitative variables, to compare between more than two groups.
IV. Kruskal Wallis test: For abnormally distributed quantitative variables, to compare between more than two studied groups.
V. Marginal Homogeneity Test: Used to analyze the significance between the different stages.
VI. Paired t-test: For normally distributed quantitative variables, to compare between two periods.
VII. Wilcoxon signed ranks test: For abnormally distributed quantitative variables, to compare between two periods.
VIII. Student t-test; For normally distributed quantitative variables, to compare between two studied groups.
IX. Mann Whitney test: For abnormally distributed quantitative variables, to compare between two studied groups.
X. Receiver operating characteristic curve (ROC): It is generated by plotting sensitivity (TP) on Y axis versus 1-specificity (FP) on X axis at different cut off values. The area under the ROC curve denotes the diagnostic performance of the test. Area more than 50% gives acceptable performance and area about 100% is the best performance for the test. The ROC curve allows also a comparison of performance between two tests.
XI. Kaplan-Meier: Kaplan-Meier Survival curve was used, and cox regression was done for the significant relation with progression free survival and overall survival.

3. Results and discussion

3.1 Demographic, clinical features of the studied groups of PAH

The total number of patients included in the study was 106. The patients were classified into their different pulmonary hypertension groups; idiopathic PAH were 30 patients (28.3%), PAH-CHD were 27 patients (25.5%), PAH due to restrictive lung disease were 35 patients (33%), and 13.2% due to other causes.

3.2 NT pro-BNP

The median level of NT-pro BNP in all patients was 851.5 with IQR from (220 to 5140.1) pg/ml. There was a statistically significant difference between the different groups regarding the serum level of NT-pro BNP, where patients in group 1.1 had higher levels of the test with a median level of 4677.5 with IQR from (1031.6 to 7706) pg/ml (P<0.001). The following table describes the comparison between the level of NT pro-BNP test between the different groups.

3.3 Relation of NT- proBNP and different clinical and echocardiographic parameters of studied patients:

There was a significant positive correlation between the following; Z score of the RV end diastolic diameter, Z score of the RA area , Z score of the main pulmonary artery diameter, tricuspid regurgitant gradient, pulmonary regurgitant gradient with the Z score of the serum level of the NT pro-BNP test [rs=0.589, P<0.001, rs=0.527, P<0.001, rs=0.424, P<0.001, rs=0.346, P=0.001, rs=0.349, P=0.001 respectively]. On the other hand, there is a significant negative correlation between the 6MWD and 2D TAPSE with the Z score of the serum level of NT pro-BNP test (rs= -0.455, P<0.001, rs= -0.433, P<0.001

respectively) (Fig1). Correlation of Z score of NT-pro BNP with WHO functional class was shown in figure 2 (Fig 2a) as WHO class 4 had a median pro- BNP z score of 5 (P=0.001).

3.4 Outcome of the studied groups

The three main outcomes reported in our series are mortality, morbidity and good outcome without history of hospital admissions during the period of the study. We had 22 mortality (19.6%) and 15 morbidity (13.4%).

NT pro-BNP was identified as a predictor of morbidity by univariate logistic regression analysis (odds ratio = 1, 95% CI = 1.0001 to 1.0003, P = 0.008). NT pro-BNP was identified as a predictor of mortality by univariate logistic regression analysis, (odds ratio = 1, 95% CI = 1.0 to 1.0, P = 0.009).

3.5 Survival probability in relation to the level of N-terminal pro-BNP

Figure (3) shows Kaplan-Meier survival curves related to the level of N terminal pro-BNP test. The mean survival was 22 months for the patients with serum levels below 4830 (86% survival) and 16 months in patients with serum levels above 4830 (59.3% survival), log-rank chi-squared=11.671, P=0.0006.

3.6 Correlations between the N terminal pro-BNP test and different parameters: (table 5)

1- There is a significant positive correlation between the z score of the RV end diastolic diameter and the serum level of the NT pro-BNP test ($\mathbf{r_s}$=0.578, P<0.001).
2- There is a significant positive correlation between the z score of the RA area and the serum level of the N terminal pro BNP test ($\mathbf{r_s}$=0.554, P<0.001).
3- There is a significant positive correlation between the 2D TAPSE and the serum level of the N terminal pro BNP test ($\mathbf{r_s}$=0.477, P<0.001).
4- There is a significant negative correlation between the 6MWD and the serum level of N terminal pro BNP test (r_s=-0.464, P<0.001).
5- There is a significant positive correlation between the WHO functional class and the serum level of N terminal pro BNP test (r_s=0.385, P<0.001).
6- There is a significant positive correlation between the TR PG (the ESPAP) and the serum level of N terminal pro BNP test (r_s=0.352, P<0.001).
7- There is a significant positive correlation between PR PG (the EDPAP) and the serum level of N terminal pro BNP test (r_s=0.320, P=0.002).
8- There is a significant positive correlation between frequency of hospital admissions and the serum level of N terminal pro BNP test (r_s=0.222, P=0.047).

Pulmonary arterial hypertension is defined as a mean pulmonary arterial pressure greater than 25 mmHg at rest, with a pulmonary artery wedge pressure less than 15 mmHg and an increased pulmonary vascular resistance greater than 3 Wood units×M2 [1].

This was a prospective observational cohort study that was conducted in the pediatric cardiology department of Cairo University Children's Hospital during the duration of the study (from January 2020 to September 2022). All patients from the age of 3 months to 18 years were included in the study. All classes of pulmonary hypertension were included except class II and patients with persistent pulmonary hypertension of the newborn.

The total number of patients included in the study was 106. 30 patients (28.3%) were idiopathic (IPAH), 27 patients (25.5%) were secondary to CHD (PAH-CHD), 35 patients (33%) were due to restrictive lung disease, 4 patients (3.8%) were secondary to obstructive upper airway disease, 6 patients (5.7%) were associated with multisystem affection, 2 patients (1.9%) were secondary to a hereditary cause (HPAH) and 2 patients were associated with portal hypertension. The etiology of pediatric pulmonary hypertension varies greatly between different studies. The TOPP (Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension) registry, a prospective multicenter study involving 55 centers in 19 countries between 2008-2010, showed that the majority of patients were diagnosed with idiopathic and hereditary pulmonary hypertension (n = 243 out of 317; 57%), followed by patients with pulmonary hypertension secondary to congenital heart disease (n = 161; 38%) [7]. The REVEAL registry, a multicenter study conducted in the United States showed that idiopathic and hereditary pulmonary hypertension were diagnosed in 122 of 216 (56%) patients and pulmonary hypertension secondary to CHD in 77 (36%) patients [8]. This is totally different from the data published by the pediatric arm of the Polish registry of pulmonary hypertension, which found that most patients (54 of 80 patients; 67.5 %) were due to pulmonary hypertension secondary to CHD and only 25 (31%) patients were due to idiopathic pulmonary hypertension [9]. Also, Zhang et al, who retrospectively studied the clinical characteristics and outcomes of the pediatric patients who visited the Beijing Anzhen Hospital from September 2008 to December 2018, revealed that 42 of 82 patients were diagnosed with hereditary pulmonary hypertension [10].

Genetic testing was not performed routinely in our hospital and in the majority of the published reports, which might be causing cases of hereditary pulmonary hypertension to be misclassified as idiopathic pulmonary hypertension. Our study included 62 females (58.5%), which was similar to 59% females in the TOPP registry, 61% females in the REVEAL registry, and 61% females in the Dutch national registry [11]., while there was an equal distribution in the pediatric arm of the Polish registry of pulmonary hypertension [9].

Table 1: Comparison between the different studied groups according to pro B natriuretic peptide

Pro B Natriuretic peptide	Total (n = 106)	Group 1.1 (n = 30)	Group 1.4.4 (n = 27)	Group 3.2 (n = 35)	Group 3.4 (n = 4)	Group 5.2 (n = 6)	P
Min. – Max.	20.0– 29102.0	20.0–15000.0	25.20–15000.0	20.0–29102.0	201.8–14133.9	193.6–5019.0	<0.001*
Mean ± SD.	3066.4±4621.7	4796.2±4205.3	3107.2±4305.5	1818.2±5172.9	4032.5±6747.6	1624.0±1838.7	
Median (IQR)	851.2 (220–5140.1)	4677.5 (1031.6–7706)	1234.1 (371.2–4113.0)	248.6 (46.0–436.3)	897.1 (385–7679.95)	817.4 (479.8–2417)	

p: p value for comparing between the different studied groups
*: Statistically significant at $p \leq 0.05$

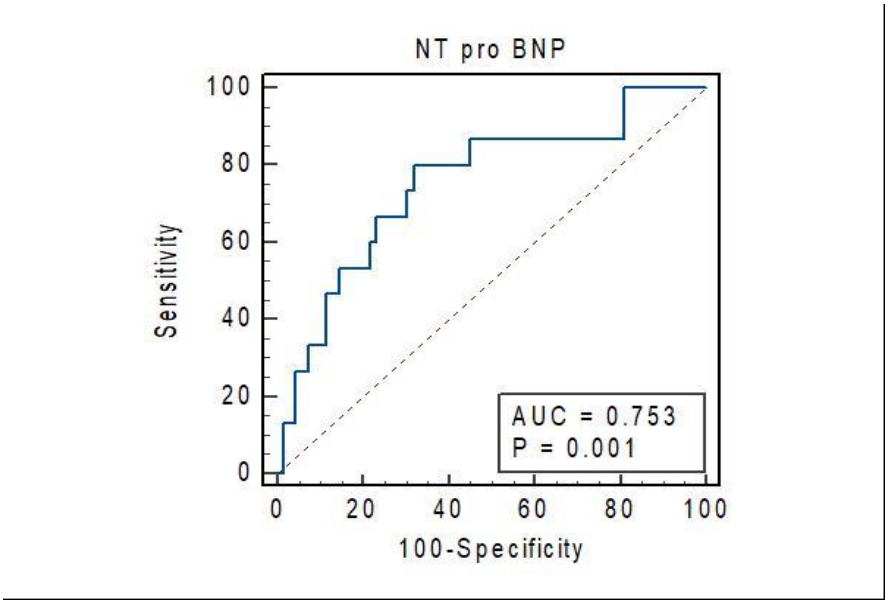

Figure 1: ROC curve analysis to predict the morbidity

Table 2: Prognostic performance of the ROC curve for the NT pro-BNP to predict the morbidity

	AUC	**P**	**95% C.I**	**Cut off**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
NT pro-BNP	0.753	0.001*	0.646 to 0.840	>1032	80	68.12	35.3	94.0

AUC: Area Under a Curve, p value: Probability value, CI: Confidence Intervals
NPV: Negative predictive value , PPV: Positive predictive value
*: Statistically significant at $p \leq 0.05$

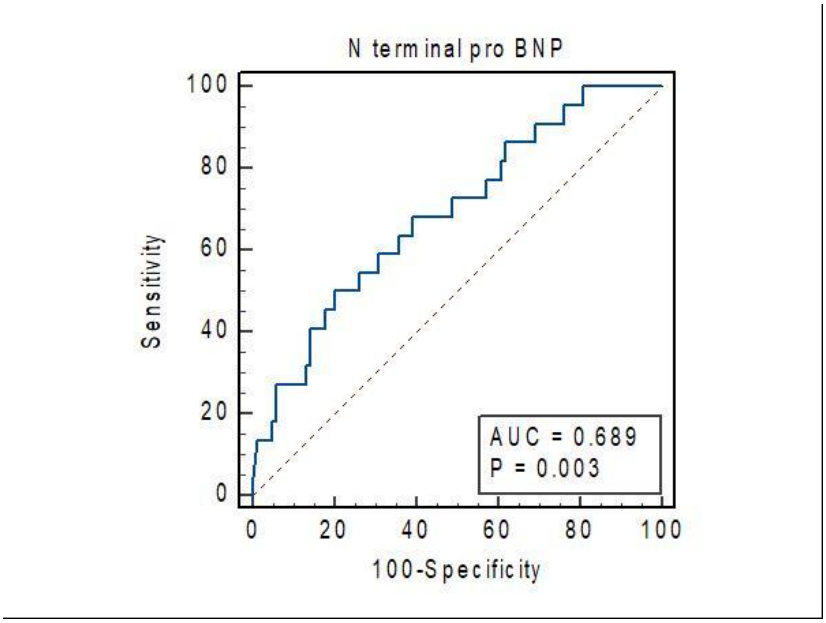

Figure 2: ROC curve analysis of the N terminal pro BNP to predict the mortality.

Table 3: Prognostic performance for the NT pro-BNP to predict the mortality

	AUC	P	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
Pro B Natriuretic peptide	0.689	0.003*	0.592 to 0.775	>4830	50.0	79.67	39.3	85.9

AUC: Area Under a Curve, p value: Probability value, CI: Confidence Intervals
NPV: Negative predictive value , PPV: Positive predictive value
*: Statistically significant at $p \leq 0.05$

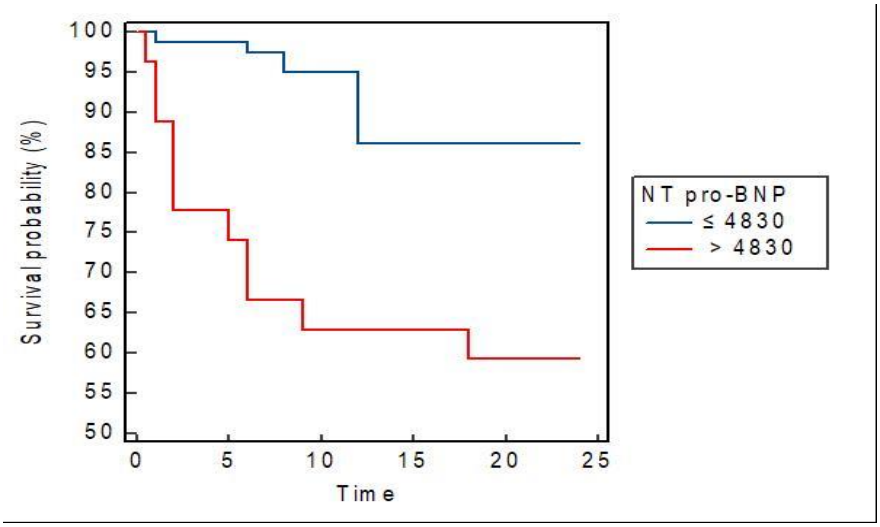

Figure 3: Kaplan-Meier survival curves related to the level of N terminal pro-BNP test

Table 4: Kaplan-Meier survival curve for overall survival with NT pro-BNP levels

NT pro-BNP	Mean	% End of study	Log rank	
			χ^2	P
Less than 4830	22	86.1	11.671	0.0006
More than 4830	16	59.3		

Table 5: Correlation between Pro B Natriuretic peptide and different parameters

Parameter	r_s	P
6MWD in meters	-0.464	<0.001*
WHO class of PH pre	0.385	<0.001*
Frequency of hospital admission	0.222	0.047*
TR PG	0.352	<0.001*
PR PG	0.320	0.002
RVEDD z score	0.578	<0.001*
RA area	0.103	0.304
RA area z score	0.554	<0.001*
MPA diameter	0.047	0.638
TAPSE	-0.477	<0.001*

r_s: Spearman coefficient

*: Statistically significant at $p \leq 0.05$

In our study, the median age of our patients was 7 years with IQR ranging from 4 to 11 years, which was consistent with the age reported in other publications that have included patients of various ethnicities, such as in the TOPP registry, where the median age was 7 years with IQR ranging from 3 to 12 years [12]. Higher ages were reported in the Polish registry of pediatric pulmonary hypertension where the median age was 10.4 years with IQR ranging from 7.9 to 15.2 years and the Dutch national registry where the median age was 8.8 years with IQR ranging from 0.3 to 18.3 years [9, 11]. Regarding the presenting symptoms, dyspnea on exertion was usually present (84%), followed by cyanosis (38.7 %), recurrent syncopal attacks (8.5 %), seizures (5.7 %), and other vague symptoms were present in 8.5%. This was consistent with most of the registries regarding dyspnea being the most common symptom.

Regarding the WHO functional class of pulmonary hypertension, the majority of our patients (59.5%) were in class 1-2, with the remainder in class 3-4. Similar distributions were found in the other registries, such as TOPP, REVEAL, and the Polish registry, with more patients in classes 1 and 2 (64%, 73%, and 68.8%, respectively). The Dutch national registry revealed the opposite, with more patients (66%) falling into class 3-4. In our study, the mean six-minute walking distance for all patients was 299.3 148.7 meters, which was lower than the results obtained from other registries. The Dutch national network reported a 6MWD mean of 342 ±91 meters [11]. TOPP, REVEAL, and the Polish registries all reported a 6MWT above 400 meters. Our patients had higher levels of N terminal pro-BNP, with a median level of 851.5 with an IQR ranging from 220 to 5140.1 pg/ml compared to the Dutch National Network of Pulmonary Hypertension, where the median level was 606 with an IQR ranging from 137 to 1830 pg/ml [11] and the Polish registry, where the median level was 272 With IQR ranging from 104.6 to 628 pg/ml [9].

In our study, there was a significant positive correlation between the NT pro-BNP and the z score of the left ventricular end-diastolic diameter, the z score of the right atrial area, the WHO functional class and the 2D TAPSE by the echocardiography; and a significant negative correlation with the 6MWD. The Dutch national network of pediatric pulmonary hypertension found that the NT pro-BNP was strongly correlated with the WHO-FC, but there was no significant correlation between the NT pro-BNP and TAPSE, mean pulmonary arterial pressure, or pulmonary vascular resistance index [11]. Regarding the treatment of pulmonary hypertension, the reversal of the advanced structural and vascular changes has not yet been achieved with current therapy, but the quality of life and survival have improved significantly. Targeted pulmonary vasodilator therapies, including endothelin receptor antagonists, prostacyclin analogs, and phosphodiesterase type 5 inhibitors have resulted in hemodynamic and functional improvement in children. The management of pediatric PAH remains challenging as treatment decisions depend largely on results from evidence-based adult studies and the clinical experience of pediatric experts [13].

In our study, 38 patients (35.8 %) received monotherapy (sildenafil), 65 patients (61.3%) received dual therapy (sildenafil and bosentan or ambrisentan) and 3 patients (2.8%) received triple pulmonary vasodilator therapy (sildenafil, bosentan and selexipag). In our study, the main line of treatment was dual pulmonary vasodilating therapy. By revising the studies of pediatric pulmonary hypertension, we noticed that the use of dual and triple pulmonary vasodilating agents had increased in the last years. The data from a large population of PAH patients aged under 18 years, treated in the US between 2010 and 2013, showed that double and triple combination therapies were used in 13.1% and 3.2% of patients, respectively [14]. In the analysis of incident PAH patients enrolled in the multinational TOPP registry, at the time of diagnosis, the

main line of treatment was the monotherapy, and the double and triple combination therapies were applied to 18% and 2.3% of patients, respectively [15]. The analysis of more recent data from the Netherlands (June 2013–March 2016) showed an increased use of double and triple combination therapies in PAH children [15 (50%) and five (17%), respectively] [16].

During the follow-up of our patients, there was a statistically significant improvement in the WHO functional class, a significant decrease in the rate of hospital admissions, and the serum level of the NT pro-BNP from a median level of 545.2 to a median level of 364.2 pg/ml. There were no statistically significant changes related to the echocardiographic parameters. So, after the initiation of medical treatment, there was a clinical improvement but still no improvement regarding the echocardiographic parameters in our study. The Dutch national network of pulmonary hypertension also observed clinical improvement, with significant improvements in the WHO functional class, 6MWD, and NT pro-BNP levels, but they also revealed a significant decrease in the RV/LV ratio after initiation of medical treatment [11]. We had 22 mortality cases (19.6%) and 15 morbidity cases (13.4%). This was a lower mortality rate than that reported by the Dutch National Network of Pulmonary Hypertension, which showed that 25 patients out of 82 (38%) died [11].

The predictors of morbidity in our study were WHO functional classes (3 and 4), recurrent syncopal attacks, the presence of RV failure, and right ventricular dilatation (cut off value of the RV/LV ratio≥ 0.93), Right atrial dilatation (cut off value of the z score of the RA area ≥2.64), high NT pro-BNP level (a cut off value of 1032 pg/ml was considered a predictor of morbidity and a level of 4830 as a predictor of mortality) and a low 6MWD (a distance ≤190 meters) and RVOT acceleration time (cut off value ≤ 74 milliseconds). The Dutch National Network of Pulmonary Hypertension reported only three predictors of worse outcomes; the WHO functional class 4, NT-pro-BNP >1200 pg/ml and TAPSE less than 12mm [11].

4. Conclusion

The N-terminal pro-BNP levels are strongly correlated with the right ventricular diameter and the right atrial area and moderately correlated with the 2D TAPSE, WHO functional class, and the 6MWD. Also, the N terminal pro BNP is a predictor of morbidity and mortality.

Conflict of interest

There are no conflicts of interest to declare.

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