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What Levels of Uric Acid and NT-Probnp Predict Outcomes of Eisenmenger Syndrome in Children?

ORIGINAL INVESTIGATION

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ABSTRACT

Objective: Noninvasive methods for follow-up of pulmonary hypertensive children are limited. The main aim of this study was to determine the cutoff levels for uric acid and N-terminal pro-brain natriuretic peptide (NT-proBNP) for follow-up of Eisenmenger patients and their relationships with classical methods. To our best knowledge, this is the first study to investigate the levels of NT-proBNP and uric acid in pediatric Eisenmenger patients.

Materials and Methods: Sixteen patients with Eisenmenger syndrome and 37 healthy children as controls were included in the study. The serum NT-proBNP and uric acid levels of the participants were measured. The echocardiography, six-minute walk test, and right cardiac catheterization data of the two groups were compared.

Results: NT-proBNP>81.4 pg/mL and uric acid >3.5 mg/dL were found to be the most specific and sensitive points for predicting the severity of pulmonary hypertension in Eisenmenger syndrome. There was no significant difference between mean pulmonary arterial pressure and serum NT-proBNP level; however, the differences between pulmonary vascular resistance and serum NT-proBNP level and between mean pulmonary arterial pressure and serum NT-proBNP level were significant. There was no significant difference between NT-proBNP level and New York Heart Association functional classification or six-minute walk test distance. There was no significant difference between serum uric acid level and pulmonary vascular resistance, right atrial pressure, or mean pulmonary arterial pressure.

Conclusion: It is too early to determine if serum biomarkers can replace classical diagnostic methods in Eisenmenger syndrome; further studies are required.

Keywords: Pulmonary hypertension, children, markers, follow-up

INTRODUCTION

Pulmonary hypertension (PHT) is a severe, progressive disease which can rapidly deteriorate if left untreated (1). The classical diagnostic and follow-up methods, such as echocardiography, catheterization, and the six-minute walk test, have some restrictions. In recent years, biomarkers are being used more commonly in the diagnosis and follow-up of PHT patients (2, 3). These are markers of heart failure, endothelial and/or platelet dysfunction, cardiac myocyte damage, and oxidative stress (2-6).

In this study, we aimed to investigate the importance of certain biomarkers in Eisenmenger patients and the relationship of these biomarkers with classical methods. To our best knowledge, this is the first study to investigate the roles of brain natriuretic peptide (BNP) and uric acid in pediatric Eisenmenger patients.

MATERIALS and METHODS

Study Population

This study was performed between May 2010 and January 2011 in the Pediatric Cardiology Clinic of Erciyes University Children's Hospital. The parents of each participant were informed about the study, and written consent was obtained. The local institutional ethics committee approved the study protocol.

Sixteen Eisenmenger patients aged 9.2±4.8 years (3 to 18 years) were included in this study. Ten of the patients were male, and six were female. The control group included patients who were admitted to the pediatric cardiology clinic for any reason and whose physical examination, electrocardiography, telecardiography, echocardiography, and laboratory investigations (complete blood count, blood glucose, serum lipids, and renal and liver function tests) were completely normal. Thirty-seven patients (17 female, 20 male) were included in the control group. The epidemiologic features of the patients are shown in Table 1.

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Blood pressure was calculated after a 15-minute resting period using an appropriately sized sphygmomanometer. Mean blood pressure (MBP) was calculated according to the following formula: MBP=DBP+(SBP–DBP)/3. Body mass index (BMI) was calculated according to the following formula: BMI=weight (kg)/height (m^2).

Blood was drawn from each case. Hemoglobin, blood urea nitrogen, uric acid, creatinine, and N-terminal pro-BNP (NT-proBNP) levels were studied. These studies were performed in the central laboratory of our university hospital using Abbot Aeroset C16000 Chemical Commercial kits. Hemoglobin was studied in the hematology laboratory using a Beckman Coulter Gen-S System 2 and is expressed as g/dL.

Five mL blood samples were drawn from both patients and controls to determine NT-proBNP levels. Blood samples were centrifuged at 4°C and 1500 rpm for 5 minutes. The plasma portion of the upper phase was transferred to another tube for NT-proBNP calculation. Samples were preserved at –80°C until the study date. Later, they were studied by the ELISA method using Biomedica NT-proBNP commercial kits (NT-proBNP enzyme immunoassay kit, Biomedica, Bratislava, Slovakia) and an Elecsys® 1010 autoanalyzer (Roche Diagnostics, Basel, Switzerland). Results were expressed as fmol/ml (1 fmol/mL=16.1 pg/mL).

Echocardiographic Evaluation

Echocardiographic examination was performed for all children in the control and Eisenmenger groups using a Vivid 7 ultrasound (GE, Horten, Norway) with a 3 MHz transducer. Investigations were performed in parasternal long, short axis, four chamber, and five chamber views using M-mode and Doppler waves. 2D measurements were performed according to the guidelines of the American Society of Echocardiography. M-mode views were obtained in the parasternal long axis by placing the cursor between the mitral valves and apical to the tips of the mitral valve leaflets. Ejection fractions and end-diastolic or end-systolic volumes were calculated using the Teicholtz (Teich) method (7).

Cardiac Catheterization

Cardiac catheterization data was obtained from the previous records of patients with Eisenmenger syndrome. Catheterization was not performed on the patients in the control group.

The pulmonary arterial mean pressure (mmHg), aortic mean pressure (mmHg), left ventricular end diastolic pressure, and the oxygen saturation of the superior vena cava (%), main pulmonary artery, and aorta were measured. Pulmonary vascular resistance (Wood units) was calculated using the equation 80×(mean pulmonary arterial pressure–pulmonary capillary pressure)/cardiac output (8).

Statistical analysis

All tests were performed using Statistical Package for Social Sciences for Windows 16.0 (SPSS Inc.; Chicago, IL, USA) and Sigma Stat 3.1. First, the distributions of all parameters were determined using the Shapiro-Wilk test. The parameters with normal distribution were expressed as mean±SD, and the parameters with abnormal distribution were expressed as median (minimum–maximum). Comparisons of means were performed by Student's t-test. Comparisons of medians were performed with the Mann-Whitney U test. Correlations were calculated with the Pearson product moment or Spearman rank order, as determined by the normalcy of data distribution. Receiver operator characteristic curve (ROC) analysis using Metlab software (version 12.5.0, Ostend, Belgium), was used to select the threshold values of NT-proBNP and uric acid values to predict PHT. The area under the ROC curve (AUC) and its standard error were calculated. Odds ratios (OR) were calculated, and the results are presented as ORs with a 95% confidence interval (CI). P-value<0.05 was accepted as statistically significant.

Table 1. General features of the patient and control groups and angiographic features of the patient group

Variable	Patient (n=16)	Control (n=37)	p
Age, years	9.2±4.8	9.1±3.1	0.876
Sex, M/F	6/10	20/17	0.268
Weight, kg	24.0±11.5	30.5±10.8	0.066
Body surface area, m^2	0.9±0.3	1.04±0.25	0.038
Height, cm	121.5±26.6	131.2±18.5	0.3
Pulse, beats/min	94.5±16.8	85.6±14.5	0.063
Systolic blood pressure, mmHg	100 (80–120)	105 (90–120)	0.002
Diastolic blood pressure, mmHg	62.5 (50–75)	60 (50–80)	0.272
Mean blood pressure, mmHg	73.4±8.3	79.2±7.8	0.018
Body mass index, kg/m^2	15±2.1	17±2.0	0.003
Pulmonary vascular resistance, U/m^2	13.4±4.4		
Pulmonary arterial mean pressure, mmHg	77.1±11.1		
Main pulmonary arterial O_2 saturation, %	78±8.8		
Right atrium pressure, mmHg	7.2 (3.5)		

F: female; M: male; SD: standard deviation

The parameters with normal distribution were expressed as mean±SD, and the parameters with abnormal distribution were expressed as median (minimum–maximum).

RESULTS

The epidemiologic features of the patients are summarized in Table 1. There were no significant differences in terms of age, sex, weight, or height of the children in the two groups. However, the body surface areas and body mass indexes were significantly lower in the Eisenmenger group. Systolic blood pressure and mean blood pressure were lower in the Eisenmenger group.

NT-proBNP and uric acid levels were significantly high in the patient group (p<0.05; Table 2). In contrast, there was no significant difference between blood urea nitrogen and creatinine level. These were in the normal range (Table 2). NT-proBNP was not correlated with pulmonary arterial pressure or right atrial pressure. A significant re-

Table 2. Biochemical features of the patient and control groups

Variable	Group: Patient (n=16)	Group: Control (n=37)	p
Blood urea nitrogen, mg/dL	12 (9–15)	11 (7–20)	0.0.177
Creatinine, mg/dL	0.6 (0.4–0.8)	0.6 (0.5–0.86)	0.106
Uric acid, mg/dL	4.9±1.7	3.5±0.8	0.006
NT-proBNP level, fmol/mL	237.9 (11.42–1171.6)	18.8 (7.73–81.4)	0.001

NT-proBNP: N-terminal pro-brain natriuretic peptide

Table 3. Correlations between N-proBNP level, serum uric acid level, and other variables

Variable	N-proBNP level, fmol/mL: R	N-proBNP level, fmol/mL: P	Serum uric acid level, mg/dL: R	Serum uric acid level, mg/dL: P
Mean pulmonary arterial pressure, mmHg	0.26	0.36	–0.04	0.87
Right atrial pressure, mmHg	0.12	0.64	–0.35	0.20
Pulmonary vascular resistance, U/m^2	0.69	0.006	0.22	0.42
NYHA functional class	0.03	0.90	0.26	0.33
6 minute walking distance, m	0.29	0.38	0.01	0.97

NT-proBNP: N-terminal pro-brain natriuretic peptide; NHYA: New York Heart Association

lationship was present between pulmonary vascular resistance and NT-proBNP (r: 0.69, P: 0.006; Table 3). A significant negative correlation was found between cardiac output and NT-proBNP (r: 0.66, p: 0.02; Table 3). A positive significant relationship was present between serum uric acid and age in the patient group (r: 0.58, P: 0.02; Table 3). The relationship between serum uric acid, NYHA functional class, and six-minute walk test distance is shown in Table 3.

NT-proBNP>81.4 pg/mL was found to be the best specificity and sensitivity point for predicting the severity of PHT in Eisenmenger syndrome. The diagnostic sensitivity, specificity, and positive predictive and negative predictive values of NT-proBNP with regard to the prediction of PHT were 80%, 100%, 100%, and 92.5%, respectively. AUC=0.897; 95% CI: 0.781–0.964; P: 0.0001 (Figure 1).

Uric acid >3.5 was found to be the best specificity and sensitivity point for predicting the severity of PHT in Eisenmenger syndrome. The diagnostic sensitivity, specificity, and positive predictive and negative predictive values of uric acid with regard to the prediction of PHT were 93.75%, 51.35%, 45.5%, and 95%, respectively. AUC=0.780, 95% CI: 0.644–0.882; P=0.0002 (Figure 2).

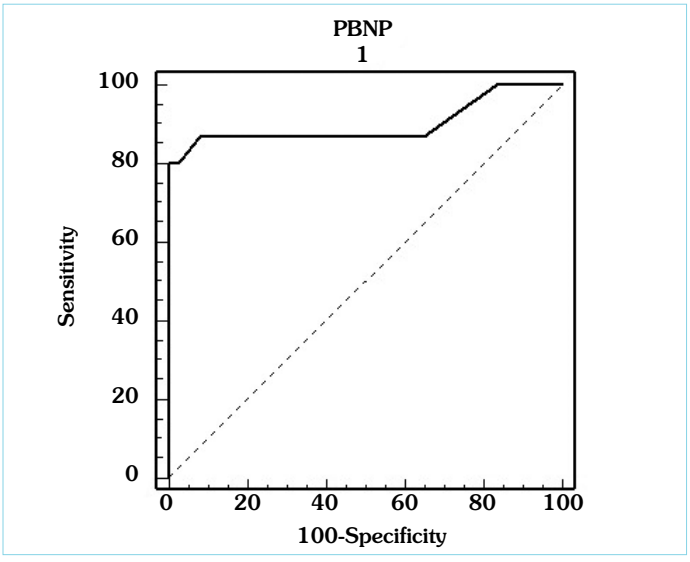

Figure 1. ROC of NT-proBNP for prediction of the severity of PHT in Eisenmenger syndrome. The plot was constructed by computing the sensitivity vs. 100-specificity for the different possible cutoff points of the serum NT-proBNP levels. AUC=0.897, 95% CI: 0.781–0.964; p=0.0001. The diagnostic sensitivity, specificity, and positive predictive and negative predictive values of NT-proBNP with regard to the prediction of PHT were 80%, 100%, 100%, and 92.5%, respectively

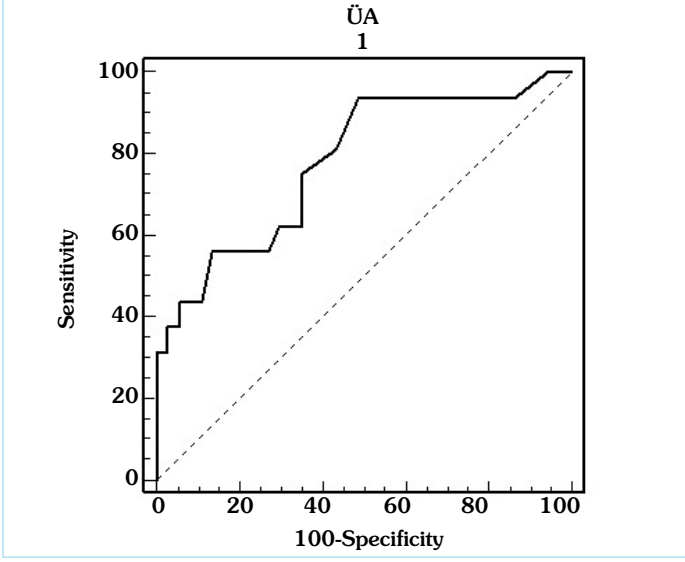

Figure 2. ROC of uric acid for prediction of the severity of PHT in Eisenmenger syndrome. The plot was constructed by computing the sensitivity vs. (100-specificity) for the different possible cutoff points of the serum uric acid levels. AUC=0.780, 95% CI: 0.644–0.882; p=0.0002. The diagnostic sensitivity, specificity, and positive predictive and negative predictive values of uric acid with regard to the prediction of PHT were 93.75%, 51.35%, 45.5%, and 95%, respectively

A pairwise comparison of the ROC curves of NT-proBNP and uric acid for the prediction of the severity of PHT in Eisenmenger syndrome was performed. The AUC for NT-proBNP was 0.897; for uric acid, it was 0.788. The standard error for NT-proBNP was

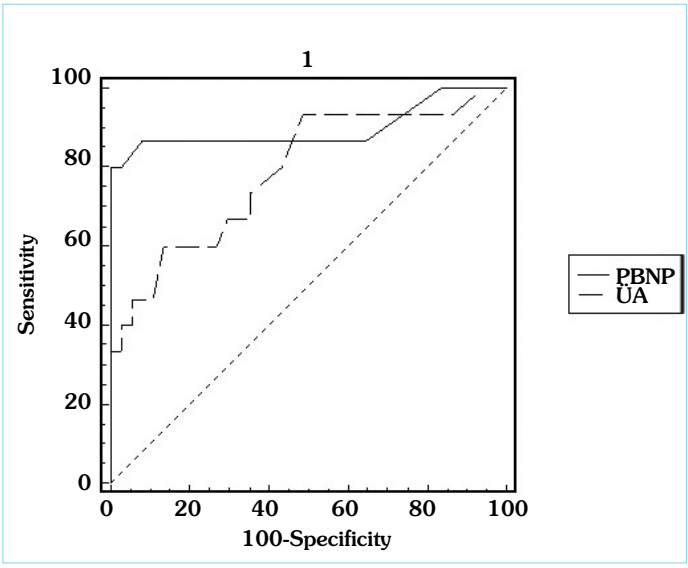

Figure 3. Pairwise comparison of ROC curves of NT-proBNP and uric acid for prediction of the severity of PHT in Eisenmenger syndrome. AUC for PBNP=0.897 and for uric acid=0.788. Standard error for PBNP=0.057 and for uric acid=0.076. 95% CI for PBNP=0.781–0.964 and for uric acid=0.653–0.889. Significance level, p=0.227

0.057; for uric acid, it was 0.076. The 95% CI for NT-proBNP was 0.781–0.964; for uric acid, it was 0.653–0.889. The significance level was found to be p: 0.227 (Figure 3). Therefore, there was no significant difference between NT-proBNP and uric acid for prediction of the severity of PHT in Eisenmenger syndrome.

DISCUSSION

Each classical test used for the follow-up of pulmonary hypertensive patients has specific limitations. Echocardiography only estimates pulmonary arterial pressure and cannot be performed in cases where tricuspid regurgitation is undetectable. Cardiac catheterization is difficult to perform, especially repetitively. The six-minute walk test is easy to perform; however, it cannot reflect the whole status of the patient and does not provide sufficient data. Also, it is not feasible and is less validated in young children (9, 10). Certain biomarkers, such as BNP, serum creatinine, and uric acid, have been used in PHT (11, 12). The most important feature of this study and its main difference from other studies is that it uses the largest Eisenmenger pediatric population to date to investigate the roles of NT-proBNP and uric acid in comparison with hemodynamic data (noninvasive and invasive) in children.

Serum creatinine level is a predictor of outcome in PHT. An increase in serum creatinine level often reflects impaired renal perfusion (13, 14). In our study, there was no relationship between creatinine level and right atrial pressure. Also, creatinine levels were low in our patients and did not increase as has been described in the literature (Table 2). The discrepancy of our study compared to the literature may be due to the poor nutritional status of our patient group.

A BNP level higher than 130 pg/mL has been found to increase heart transplantation requirement and mortality risk in pulmonary hypertensive patients (15, 16). In our study, NT-proBNP >81.4 was found to be the most specific and sensitive point for predicting the severity of PHT in Eisenmenger syndrome.

NT-proBNP concentration can be used as an alternative to the six-minute walk test to assess the severity of heart failure, especially in children who are less than six years old or who are uncooperative. Some studies show good correlations between the six-minute walk test and BNP level (17). However, we did not obtain the same correlation in our study. This may be due to the limited number of subjects; four of our subjects had Down syndrome, and three patients were less than six years of age and were uncooperative during the test.

The role of NT-proBNP in Eisenmenger patients has previously been studied in adults. However, no studies have been performed in children. To the best of our knowledge, our study is the first to investigate the role of NT-proBNP in pediatric Eisenmenger patients.

Reardon et al. (18) studied the usefulness of serum brain natriuretic peptide to predict adverse events in adult patients with Eisenmenger syndrome. Elevated serum NT-proBNP levels were predictive of adverse clinical events. Also, it was found that serum NT-proBNP was much more reliable than assessment of the right ventricular ejection fraction by echocardiography in prognosis determination. However, the relationship between NT-proBNP and catheterization findings was not studied. The only study in children was performed by Toyono et al. (19); they investigated the role of NT-proBNP in 29 patients with VSD and severe PHT. Only four patients showed apparent Eisenmenger physiology. There was a significant positive correlation between Qp/Qs and NT-proBNP. In contrast, there were significant negative correlations between BNP and PVR.

Pulmonary Hypertension severity correlates inversely with cardiac output and directly with pulmonary vascular resistance and right atrial pressure, illustrating the importance of accurate measurement of hemodynamic status to define the clinical profiles of patients (10). In our study, a positive correlation was found between PVR and NT-proBNP; however, no significant relationship was found between pulmonary artery pressure and NT-proBNP or between right atrial pressure and NT-proBNP (Table 3).

In previous studies, uric acid was found to have a positive predictive value in mortality determination of patients with chronic heart failure (20-22). The uric acid level of our patient group was found to be statistically significant.

The mortality risks of people with high serum uric acid levels (male 8.9 mg/dL and female 6.4 mg/dL) are greater than those of people with low uric acid levels (22, 23). In our study, uric acid >3.5 was found to be the most specific and sensitive point for predicting severity of PHT in Eisenmenger syndrome (Figure 2). Serum uric acid levels were also correlated with right atrial pressure, NYHA functional class, six-minute walk test, cardiac index, cardiac output, and survival (24, 25). Van Albada et al. (11) found the strongest correlations between serum uric acid and mean pulmonary arterial pressure, pulmonary vascular resistance, and cardiac index. In our study, no correlation was shown between uric acid level and NYHA functional class or six-minute walk test (Table 3). This is believed to be due to the heterogeneous distribution of underlying heart diseases of the patients and to their age distribution.

A pairwise comparison of the ROC curves of NT-proBNP and uric acid for the diagnosis of PHT was performed in our study. NT-proBNP was found to be more specific than uric acid; however, the significance level was p=0.227. Therefore, there was no significant difference between NT-proBNP and uric acid for the prediction of PHT (Figure 3).

Study Limitations

The main limitation of our study is that NT-proBNP and uric acid levels can be affected by many other factors, including left and right heart dimensions and stroke volume. Therefore, it is very difficult to make correlations with pulmonary arterial hypertension only.

The second limitation is that the underlying congenital heart defects in Eisenmenger syndrome were not the same in each case. Each patient had a different natural history and hemodynamic status.

The third limitation is that the number of patients in the Eisenmenger group was limited. Another limitation of our study is that catheterization could not be performed for the control group. We were unable to compare the invasive pulmonary artery, right atrial pressure, pulmonary arterial saturation, and pulmonary vascular resistance data of Eisenmenger patients with the control group.

In addition, these values may change with time; therefore, if follow-up could be performed, the results would be more valuable.

CONCLUSION

Our study showed that as in adults, NT-proBNP and uric acid can be used as biomarkers for follow-up of children with Eisenmenger syndrome. However, it is too early to determine if serum biomarkers can replace classical diagnostic and follow-up methods (echocardiography, angiography, six-minute walk test) in pulmonary hypertension. Some of the results of our study are not consistent with the literature, which shows that the study of biomarkers requires more time and effort. More studies with broad participation and long-term follow up should be performed.

Ethics Committee Approval: Ethics committee approval was received for this study from local ethics committee.

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Authors' Contributions: Conceived and designed the experiments or case: NA, AB, KU. Performed the experiments or case: ÖP, EY. Analyzed the data: MA, AO. Wrote the paper: ÖP, EY. All authors have read and approved the final manuscript.

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REFERENCES

1. Kurzyna M, Araszkiewicz A, Błaszczak P, Grabka M, Hawranek M, Kopeć G, et al. Summary of recommendations for the haemodynamic and angiographic assessment of the pulmonary circulation. Joint statement of the Polish Cardiac Society's Working Group on Pulmonary Circulation and Association of Cardiovascular Interventions. Kardiol Pol 2015; 73(1): 63-8. [CrossRef]
2. Jardim C, Souza R. Biomarkers and prognostic indicators in pulmonary arterial hypertension. Curr Hypertens Rep 2015; 17(6): 556. [CrossRef]
3. Heresi GA. Clinical perspective: biomarkers in pulmonary arterial hypertension. Int J Clin Pract Suppl 2011; 169: 5-7. [CrossRef]
4. Siekmeier R, Grammer T, März W. Role of oxidants, nitric oxide, and asymmetric dimethylarginine in endothelial function. J Cardiovasc Pharmacol Ther 2008; 13(4): 279-97. [CrossRef]
5. Sanli C, Oguz D, Olgunturk R, Tunaoglu FS, Kula S, Pasaoglu H. Elevated homocysteine and asymmetric dimethyl arginine levels in pulmonary hypertension associated with congenital heart disease. Pediatr Cardiol 2012; 33(8): 1323–31. [CrossRef]
6. Takatsuki S, Wagner BD, Ivy DD. B-type natriuretic peptide and amino-terminal pro-B-type natriuretic peptide in pediatric patients with pulmonary arterial hypertension. Congenit Heart Dis 2012; 7(3): 259-67. [CrossRef]
7. Palmieri V, Manganelli F, Russo C, Gagliardi B, Pezzullo S, Gagliardi G et al. Accuracy and feasibility of simplified Doppler-based left ventricular ejection fraction. Am J Cardiol 2013; 112(6): 889-94. [CrossRef]
8. Maron BA. Hemodynamics should be the primary approach to diagnosing, following, and managing pulmonary arterial hypertension. Can J Cardiol 2015; 31(4): 515-20. [CrossRef]
9. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest 2001; 119(1): 256–70. [CrossRef]
10. Savarese G, Paolillo S, Costanzo P, D'Amore C, Cecere M, Losco T, et al. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. J Am Coll Cardiol 2012; 60(13): 1192–201. [CrossRef]
11. Van Albada ME, Loot FG, Fokkema R, Roofthooft MT, Berger RM. Biological serum markers in the management of pediatric pulmonary arterial hypertension. Pediatr Res 2008; 63(3): 321-7. [CrossRef]
12. Howard LS. Prognostic factors in pulmonary arterial hypertension: assessing the course of the disease. Eur Respir Rev 2011; 20(122): 236–42. [CrossRef]
13. Sargento L, Longo S, Lousada N, Dos Reis RP. Nt-ProBNP, Anaemia and Renal function are independent predictors of hospitalization in outpatients with pulmonary artery hypertension. Rev Port Pneumol (2006) 2015; 21(1): 46-7. [CrossRef]
14. Shah SJ, Thenappan T, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Association of serum creatinine with abnormal hemodynamics and mortality in pulmonary arterial hypertension. Circulation 2008; 117(19): 2475-83. [CrossRef]
15. Das BB, Raj S, Solinger R. Natriuretic peptides in cardiovascular diseases of fetus, infants and children. Cardiovasc Hematol Agents Med Chem 2009; 7(1): 43-51. [CrossRef]
16. Casserly B, Klinger JR. Brain natriuretic peptide in pulmonary arterial hypertension: biomarker and potential therapeutic agent. Drug Des Devel Ther 2009; 3: 269-87.
17. Niedeggen A, Skobel E, Haager P, Lepper W, Mühler E, Franke A. Comparision of the 6-minute walk test with established parameters for assesment of cardiopulmonary capacity in adults with complex congenital cardiac disease. Cardiol Young 2005; 15(4): 385-90. [CrossRef]
18. Reardon LC, Williams RJ, Houser LS, Miner PD, Child JS, Aboulhosn JA. Usefulness of serum brain natriuretic peptide to predict adverse events in patients with the Eisenmenger syndrome. Am J Cardiol 2012; 110(10): 1523-6. [CrossRef]

19. Toyono M, Harada K, Tamura M, Aoki-Okazaki M, Shimada S, Oyamada J, et al. Paradoxical relationship between B-type natriuretic peptide and pulmonary vascular resistance in patients with ventricular septal defect and concomitant severe pulmonary hypertension. Pediatr Cardiol 2008; 29(1): 65-9. [CrossRef]
20. Dhaun N, Vachiery JL, Benza RL, Naeije R, Hwang LJ, Liu X, et al. Endothelin antagonism and uric acid levels in pulmonary arterial hypertension: clinical associations. J Heart Lung Transplant 2014; 33(5): 521-7. [CrossRef]
21. Baldus S, Köster R, Chumley P, Heitzer T, Rudolph V, Ostad MA, et al. Oxypurinol improves coronary and peripheral endothelial function in patients with coronary artery disease. Free Radic Biol Med 2005; 39(9): 1184-90. [CrossRef]
22. Hayabuchi Y, Matsuoka S, Akita H, Kuroda Y. Hyperuricaemia in cyanotic congenital heart disease. Eur J Pediatr 1993; 152(11): 873-6. [CrossRef]
23. Kanbay A, Inonu H, Solak Y, Erden A, Uslu E, Yuksel SA, et al. Uric acid as a potential mediator of cardiovascular morbidity in obstructive sleep apnea syndrome. Eur J Intern Med 2014; 25(5): 471-6. [CrossRef]
24. Zharikov SI, Swenson ER, Lanaspa M, Block ER, Patel JM, Johnson RJ. Could uric acid be a modifiable risk factor in subjects with pulmonary hypertension? Med Hypotheses 2010; 74(6): 1069-74. [CrossRef]
25. Oya H, Nagaya N, Satoh T, Sakamaki F, Kyotani S, Fujita M, et al. Haemodynamic correlates and prognostic significance of serum uric acid in adult patients with Eisenmenger syndrome. Heart 2000; 84(1): 53-8.[CrossRef]