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Factors Influencing Survival in Patients with Pulmonary Hypertension: a Review from Single Pulmonary Hypertension Center Registry Baseline Data

VEIKSNIAI, ĮTAKOJANTYS SERGANČIŲJŲ PLAUTINE HIPERTENZIJA IŠGYVENAMUMĄ: PLAUTINĖS HIPERTENZIJOS CENTRO REGISTRO PRADINIŲ DUOMENŲ APŽVALGA

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Summary. *Pulmonary hypertension (PH) – is a severe progressive disease leading to the right heart failure. The survival of these patients ranges from several months to several years.* ***The aim of the study:*** *to investigate factors influencing PH patient survival.* ***Matherial and methods.*** *Data from the medical charts from the Hospital of Lithuanian University of Health Sciences Kauno klinikos (Kauno klinikos) PH center were retrospectively analyzed and 59 cases of adult patients diagnosed with PH confirmed by right heart catheterization during the period 2010–2017 were included into the study (18 men and 41 women). The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS), version 20.0. P values of <0.05 were considered to indicate statistical significance.* ***Results.*** *Mean patient age was 59 years. Mean of overall survival of all cases was 50 months and was higher for patients with N-terminal B-type natriuretic peptide (NT-proBNP) ≤1,500 ng/l, than for patients with NT-proBNP>1,500 ng/l. Risk of death was five times higher in patients with NT-proBNP>1,500 ng/l, comparing with the patients with NT-proBNP≤1,500 ng/l. The shortest survival was in PH associated with connective tissue disease group. The risk of death was lower in IPAH and Eisenmenger's syndrome group, comparing with PH associated with connective tissue disease (CTD). Worse survival was associated with right ventricular (RV) enlargement and severity of tricuspid regurgitation (TR) at the baseline.* ***Conclusions.*** *According to our data, PH associated with CTD, higher baseline NT-proBNP concentration and severe RV enlargement as well as greater TR are associated with worse survival and higher risk of death in PH.*
Key words: *pulmonary hypertension, risk factors, survival.*

Santrauka. *Plautinė hipertenzija (PH) – sunki ir progresuojanti liga, sąlygojanti dešiniosios širdies nepakankamumą. Šia liga sergančių pacientų išgyvenamumas paprastai svyruoja nuo kelerių mėnesių iki keleto metų.* ***Tikslai.*** *Nustatyti veiksnius, lemiančius sergančiųjų PH išgyvenamumą.* ***Tyrimo metodai.*** *Retrospektyviai analizuoti Lietvos sveikatos mokslų universiteto ligoninės Kauno Klinikų PH centro medicininių dokumentų duomenys. Į tyrimą įtraukti 59 suaugusieji, kuriems PH diagnozė patvirtinta atliekant dešiniosios širdies kateterizaciją nuo 2010 iki 2017 metų (18 vyrų ir 41 moteris). Statistinė analizė atlikta naudojant Socialinių mokslų statistinį paketą (SPSS), 20.0 versiją. P reikšmė <0,05 pasirinkta kaip statistiškai reikšminga.* ***Rezultatai.*** *Tiriamųjų amžiaus vidurkis buvo 59 metai. Vidutinis išgyvenamumas siekė 50 mėnesių ir buvo didesnis pacientams, kurių aminoterminalinis pro-B tipo natriurezinis peptidas (NT-proBNP) ≤1500 ng/l, palyginus su pacientais, kurių NT-proBNP>1500 ng/l. PH pacientams, kurių NT-proBNP koncentracija >1500 ng/l, stebėta penkis kartus didesnė mirties rizika palyginus su pacientais, kurių NT-proBNP koncentracija buvo ≤1500 ng/l. Sergančiųjų jungiamojo audinio ligų sąlygota PH išgyvenamumas buvo trumpiausias. Rizika numirti buvo mažesnė idiopatinės plaučių arterijos hipertenzijos (IPAH) ir Eizenmengerio sindromo grupėse, palyginus su PH, sąlygota jungiamojo audinio ligų. Blogesnį PH pacientų išgyvenamumą lėmė dešiniojo skilvelio (DS) padidėjimas ir didesnis triburio vožtuvo regurgitacijos laipsnis nustatyti ligos pradžioje.* ***Apibendrinimas.*** *Remiantis tyrimo duomenimis, jungiamojo audinio ligų sąlygota PH, didelė pradinio NT-proBNP koncentracija kraujyje, ženkliai padidėjęs DS bei ryškus triburio vožtuvo nesandarumas nustatyti ligos pradžioje yra susiję su blogesniu sergančiųjų PH išgyvenamumu bei didesne mirties rizika.*
Reikšminiai žodžiai: *plautinė hipertenzija, rizikos veiksniai, išgyvenamumas.*

INTRODUCTION

Pulmonary hypertension (PH) is a rare disorder that embraces a diversity of diseases with the increase in mean pulmonary arterial pressure (PAPm) ≥25 mm Hg at rest, as assessed by right heart catheterization. Usually progressive pulmonary vascular remodelling and increased right ventricular afterload lead to right heart failure. Regardless of new medications and interventional therapy possibilities the survival of PH patients ranges from several months to several years [1, 2]. The discussions about optimal PH treatment is still ongoing and choosing the right strategy for the right patient sometimes might be a complicated task despite of all new existing and available treatment options. It is believed that risk scores enable to personalise the risk of each patient thus optimisation as well as individualisation of therapeutic strategies can be reached. According to 2015 ESC/ERS PH guidelines regular assessment of multiple variables is recommended. While many studies and analysis investigating the survival and risk of death factors in PH patients have been performed in other countries this has never been done in Lithuania. The aim of this study was to investigate the possible factors (gender, age during PH diagnosis, etiology, baseline N-terminal B-type natriuretic peptide (NT-proBNP) level, heart ultrasound data and six-minute walk test (6MWT)) affecting the mortality and survival of PH patients from PH center of Hospital of Lithuanian university of Health Sciences Kaunas Clinics.

METHODS

Data from the medical charts from the PH center of Hospital of Lithuanian University of Health Sciences Kauno klinikos (Kauno klinikos) were collected and retrospectively analyzed. The research protocol was approved by the Regional Biomedical Research Ethics Committee of the Lithuanian University of Health Sciences (Nr. BE-2-20). The study started Jan 2015 and finished Dec 2017.

Study population

59 cases of adult patients diagnosed with PH during the period 2010–2017 were included into the study (18 men and 41 women) of which 15 patients with idiopathic pulmonary artery hypertension (IPAH), 16 patients with PH associated with connective tissue disease (CTD), 10 patients with PH associated with Eisenmenger's syndrome and 18 patients with chronic thromboembolic pulmonary hypertension (CTEPH). All study patients were diagnosed with precapillary PH with mean pulmonary artery pressure (PAPm) ≥25 mm Hg, pulmonary capillary wedge pressure ≤15 mm Hg and pulmonary vascular resistance ≥3 Wood units during right heart catheterization (RHC) test. In all cases, informed consent was obtained using a written consent form and was signed by the alive study individuals. The patients who died before the study were included into the data analysis with the permission of the Regional Biomedical Research Ethics Committee of the Lithuanian University of Health Sciences.

Influence of gender, age (years) during diagnosis, etiology, baseline NT-proBNP level (ng/l), baseline 6MWT result (meters), and baseline echocardiography data on survival (months) and mortality of PH patients were assessed. The time of RHC, that confirmed PH diagnosis, was considered to be the time of diagnosis. The results of NT-proBNP test, 6MWT and heart ultrasound that were performed in two months period before or after the diagnosis establishment were taken as the baseline.

Statistical analysis

The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS), version 20.0. The normality assumption of data was verified with the Shapiro-Wilks test. The data that were distributed not normally were presented as median and ranges or interquartile range. Continuous variables were described as mean ± SD or ± SEM. For skewed distribution of the variables nonparametric tests were used. The Kaplan-Meier method with the log-rank test and *Cox proportional hazards model* were used to calculate survival rates, differences in survival curves and estimate the risk of death. Multivariable analysis for mortality was performed. *P* values of <0.05 were considered to indicate statistical significance.

RESULTS

Mean overall survival of all selected PH patients was 50 months (95% CI 40–59). 30 patients died (IPAH n=7, CTD n=12, PH associated with Eisenmenger's syndrome n=2, CTEPH n=9) during the seven-year period. The cause of death varied among the patients. The most common pathologies related with the death were progressive severe heart failure, thrombosis (stroke, infarction, pulmonary embolism), severe infections and sepsis (Table 1). The shorter survival was seen in PH associated with CTD group comparing with IPAH and Eisenmenger's syndrome group (31 months (95% CI 18–44) vs. 56 months (95% CI 41–71), p=0.028 vs. 77 months (95% CI 59–96), p=0.008 accordingly) (Figure 1-B). The risk of death was found to be three times lower for patients with IPAH (p=0.039) and six times lower for patients with Eisenmenger's syndrome (p=0.017), comparing with PH associated with CTD. By the way mean survival between IPAH, CTEPH and Eisenmenger's syndrome patients did not differ.

In order to see if NT-proBNP has any prognostic implications, we divided patients into two groups: the

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Table 1. The cause of death of pulmonary hypertension patients from the Lithuanian University of Health Sciences Kauno klinikos PH center during 2010–2017

Cause of death	IPAH (n=7)	CTEPH (n=9)	Eisenmenger's syndrome (n=2)	CTD-PH (n=12)	Total (n=30)
Severe infection	2	3	0	4	9
Progressive heart insufficiency	4	1	2	1	8
Thrombosis	0	1	0	4	5
Oncology	0	1	0	2	3
Endartherectomy	0	2	0	0	2
Unknown	1	1	0	1	3

Abbreviations: CTEPH – chronic thromboembolic pulmonary hypertension; CTD – PH – associated with connective tissue disease; IPAH – idiopathic pulmonary arterial hypertension.

Table 2. Demographic data of study patients.

	IPAH (n=15)	CTEPH (n=18)	Eisenmenger's syndrome (n=10)	CTD-PH (n=16)	Total (n=59)
Age (years), mean ± SEM	58 ± 3	65 ± 3	47 ± 5	59 ± 3	59 ± 2
Gender (male/female), n	3/12	7/11	5/5	3/13	18/41
Survival (months) mean ± SEM	56 ± 8	45 ± 9	77 ± 9	31 ± 7	50 ± 5
6MWT (metres), median (range)	312 (30–540)	315 (90–470)	240 (50–406)	208 (70–510)	289 (30–540)
NT-proBNP (ng/l), median (range)	1,473 (127–6,963)	4,206 (763–28,191)	948 (58–5,616)	2,384 (315–16,912)	1,783 (58–28,191)
WHO functional class (I-II / III-IV), n	6/9	8/10	4/6	3/13	21/38

Abbreviations: CTEPH – chronic thromboembolic pulmonary hypertension; CTD – PH – associated with connective tissue disease; IPAH – idiopathic pulmonary arterial hypertension; NT-proBNP – baseline N-terminal B-type natriuretic peptide concentration; SD – standard deviation; SEM – standard error of mean; WHO – baseline World Health Organization functional class; 6MWT – baseline 6 minute walk test.

group with NT-proBNP ≤1,500 ng/l and the group NT-proBNP>1,500 ng/l. Our data showed that mean survival was higher in group with NT-proBNP≤1,500 ng/l (70 months (95% CI 60–80)) compared to group with NT-proBNP>1500 ng/l (38 months (95% CI 24–51)) (p=0.002) (Figure 1-A). Risk of death was five times higher (95% CI Exp(B) 1.6–14.4) in patients with NT-proBNP>1,500 ng/l, comparing with the patients with NT-proBNP≤1,500 ng/l (p=0.006).

When analysing echocardiographic data of our selected PH patients, only right ventricular (RV) enlargement and severity of tricuspid regurgitation (TR) were found as independent predictors of survival (p=0.001 and p=0.025 accordingly). Surprisingly we did not found any correlation between the left ventricular ejection fraction (p=0.625), tricuspid annular plane systolic excursion (TAPSE) (p=0.114), pulmonary *velocity acceleration time* (PVAT) (p=0.377), pericardial effusion existence (p=0.557) and survival. However mean survival was higher in group of patients with RV<45 mm compare to the patient group with RV>45 mm (62 months (95% CI 50–74) vs. 26 months (95% CI 20–32), p=0.001) (Figure 1-C). Also we observed the

higher survival of patients with I–II° TR compared to the patients with III-IV° TR (56 months (95% CI 46–74) vs. 36 months (95% CI 26–46), p=0.025) (Figure 1-D).

Furthermore, the gender and the age at the diagnosis as well as baseline 6MWT result according to our data did not have any impact on PH patient survival. All demographic data are shown in detail in Table 2.

DISCUSSION

We presented the first baseline data evaluating the survival and the death risk predicting factors of Lithuanian PH patient population. As there still remain many discussions and disagreements on consensus of factors that predict mortality and prognosis in patients with PH, we choosed to retrospectively analyse data from single university hospital PH center.

Etiology

Our study has shown that the only etiology – PH associated with CTD had importance to the PH patient survival. The data revealed shorter survival in PH associated with CTD patient group comparing with IPAH and Eisenmenger's syndrome groups.
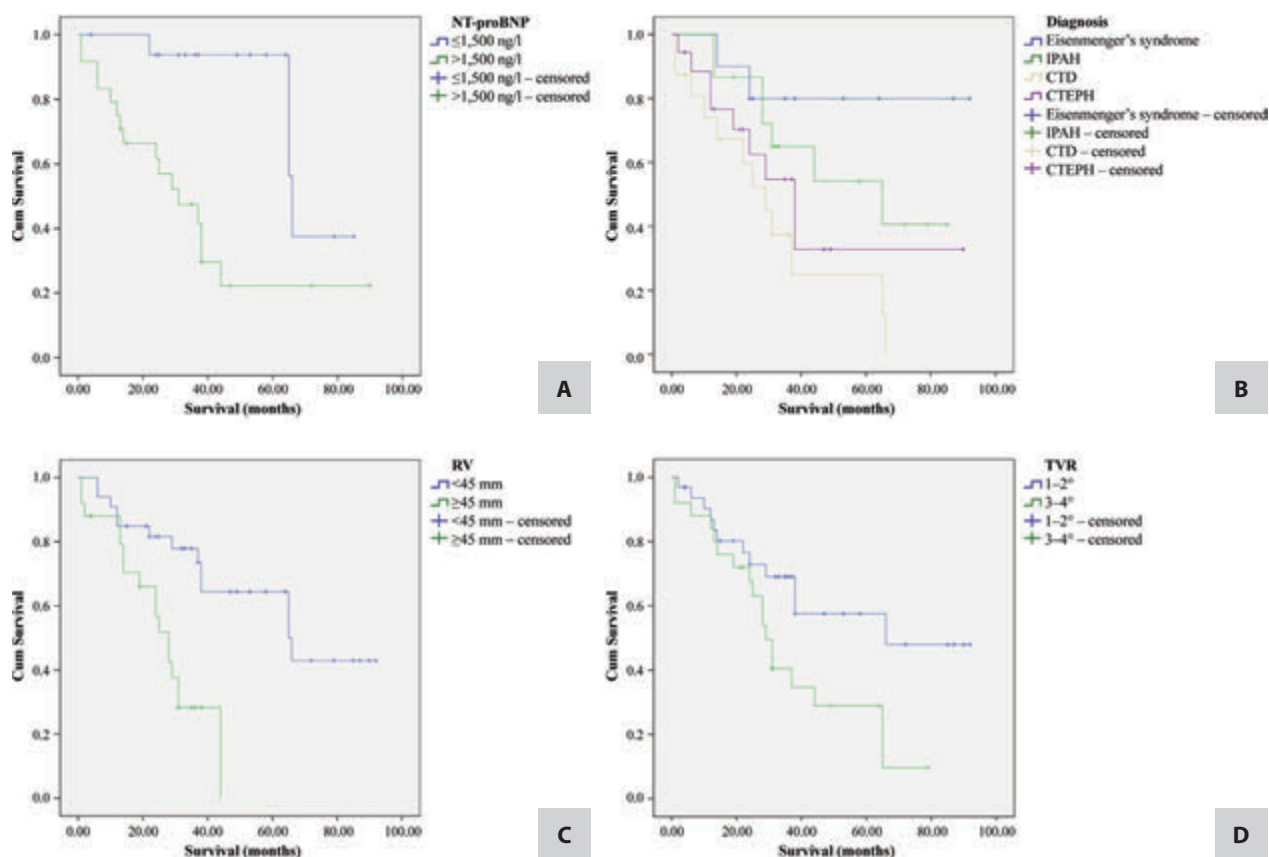
Figure 1. Survival curves according to NT-proBNP, pulmonary hypertension ethiology, RV size and TR: A – Kaplan Meier survival curve according to the serum NT-proBNP concentration. B –Kaplan Meier survival curve according to the pulmonary hypertension ethiology. C – Kaplan Meier survival curve according to the RV size. D – Kaplan Meier survival curve according to the TR.

Abbreviations: CTEPH – chronic thromboembolic pulmonary hypertension; CTD – pulmonary hypertension associated with conective tissue disease; IPAH – idiopathic pulmonary arterial hypertension; NT-proBNP – baseline N-terminal B-type natriuretic peptide concentration; RV – right ventricular; TR – tricuspid regurgitation.

Furthermore, the risk of death was lower for patients with IPAH and with Eisenmenger's syndrome, comparing with PH associated with CTD. Similar results were shown by the study where data from REVEAL registry were analyzed. They found that PH associated with CTD patients (n=641; 68% systemic scleroderma (SSc)), compared with IPAH patients (n=1251) had significantly worse one-year survival (p<0.01) [3]. Meanwhile the data from REVEAL registry also suggested that despite the differences of hemodynamic values between cohorts of PH associated with Eisenmenger's syndrome, IPAH or heritable PAH, 4 years survival was similar in all groups [4]. In another recent large study where 484 patients were enrolled, patients with PH associated with CTD (n=114) also had higher risk of death compare to those with either IPAH (n=272) or PH associated with other disease (n=98) (p<0.001) [5]. Kunieda et al. found that CTEPH patients had better survival results than IPAH patients [6]. Diller et al. in meta-analysis, where 12 studies since 1971 to 2013 were included with total 1,131 patients showed that patients with PH associated with

Eisenmenger's syndrome did not have differences in survival when comparing total life span [7].

NT-proBNP

For PH patients usually the initial cause of death is right ventricular dysfunction and failure. NT-proBNP is known to be more stable molecule than the active brain natriuretic peptide (BNP) in vivo as well as in vitro [8] and it is proved that NT-proBNP concentration is related with right heart function [9]. Recently Fijalkowska et al. showed that serum NT-proBNP level of ≥1,400 ng/l correlates with poor long-term PH prognosis [10]. At about the same time Blyth et al. from University of Glasgow also published the data that serum NT-proBNP concentration >1,685 ng/l suggests right ventricular systolic dysfunction in PH [11]. Likewise results got Gert-Jan Mauritz et al. showing that serum NT-proBNP concentration greater than 1,256 ng/l is associated with increased mortality. Furthermore, they stated that a decrease of NT-pro-BNP more than 15% per year was associated with survival [12]. Meanwhile Suntharalingama et al. showed that

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on patients with operable CTEPH NT-proBNP can be used in pre-operative evaluation for risk evaluation, either in post-operative period NT-proBNP correlates with disease progression as well as with the right ventricular function [13]. Our study results also showed that higher concentration of serum NT-proBNP (>1,500 ng/l) was strongly associated with lower PH patient survival and higher risk of death.

6MWT

While the main characteristic of PH is exercise intolerance, measurement of exercise capacity takes great place in evaluation of PH patients. 6MWT is considered to be a relevant test for exercise capacity and a good indicator of patient ability to perform daily activities [14]. However, our study did not show any correlations between survival and 6MWT. Meanwhile the number of studies with greater quantity of cases showed the importance of 6MWT as an indicator of death risk in PH: Humbert et al. after multiple analysis of French registry confirmed, that reduced 6MWT demonstrates exercise limitation and is an excellent predictor of death in PAH [15]. Farber et al. analysed the data from REVEAL registry and showed that decreasing of 6MWT was strongly and significantly associated with decreased survival and poor prognosis, but by contraries improvement of 6MWT did not had any prognostic values [16]. According to the latest ESC/ERS guidelines, 6MWT≥440 m indicates low risk (<5%) and better prognosis, whereas a 6MWT<165 m indicates high risk (>10%) and is associated with poor prognosis however 6MWT results should always be interpreted taking into account all the clinical context [17].

Echocardiography

The echocardiography is non – invasive test that provides information about anatomic abnormalities as well as hemodynamic values of right heart and pulmonary circulation that are important not just in PH diagnostic, but also in predicting survival and making therapeutic decisions [18]. In our study only, RV enlargement and severity of TR were revealed as independent predictors of mortality in patients with PH. Our study results might be limited by a small patient number and different test protocols. In series of studies the significance of echocardiography in predicting survival of PH patients was displayed. Jola Klosi et al. showed the relation between mortality and TAPSE (p=0.008), right ventricle ejection fraction (p=0.01) and pulmonary vascular acceleration time (p=0.001) [19]. Several large studies revealed moderate or severe TR and the presence of pericardial effusion as independent predictors of mortality [20, 21].

Who functional class, age and gender

It is believed that the World Health Organization (WHO) functional class remains one of the most powerful predictors of survival at diagnosis as well as during follow-up. A worsening functional class proved to be one of the most alarming indicators of disease progression. Actually, our data showed only the tendency of WHO functional class being related with survival and risk of death however these data might be limited again by the small patient number included into the study. Our study results did not show any association between survival and age or gender. Very similar data were presented by NIH Registry. That was the first large-scale registry, where prognostic factors such as age and gender were not associated with survival in IPAH [18]. In Israel a national survey of IPAH data of 44 patients was performed. According to its data neither the age nor gender was associated with the survival [22]. A decade ago Miyamoto et al. presented data from the study were among the non-invasive variables of 43 patients with IPAH that were studied, age and gender also did not have any association with the PH patient survival [23].

Meanwhile the study where the data from REVEAL registry was used with 2716 cases included showed that men older than 60 years were independently associated with higher death risk (HR, 2.2; 95% CI 1.6–3.0), comparing with the men younger than 60 years and also with the women group [24]. According to the data from Spain REHAP registry the univariate analysis showed that male sex and age were associated with higher risk of death and poor outcomes, however after multiple analyses only male sex remained as independent predictor of death [25]. In a retrospective study of single center in India, 61 cases with IPAH were analysed and younger age was found as predictor of poor prognosis and death. It should be noted that this population was younger than that included in the NIH Registry [21, 26].

The major limitation of our study was small study population. There are only less than three million people in Lithuania and two PH centers without overall registry. Our PH center performs all diagnostic procedures and offers professional follow-up as well as the treatment for half of Lithuania, so part of the patients suspected or diagnosed with PH might go to another center. Furthermore, patients that are suspected with PH but have multiple comorbidities or high age may never be sent to PH center from local hospitals. The second limitation – while only baseline data were analyzed, PH treatment was not taken into account. Probably because of these limitations the association between survival and factors, that were revealed as associated with survival and risk of death in other, larger

cohort studies, were not found. Establishing of national or Baltic countries registry would provide better knowledge of this progressive and fatal disease. Further analysis of possible risk factors should be performed taking into account the treatment that was applied.

CONCLUSION

Our data suggests that the survival and risk of death of PH patients are associated with disease etiology, RV enlargement, TR severity and NT-proBNP level at the baseline. However, some independent predictors of mortality and survival were not identified probably because of the limitations of the study – small population and heterogeneity of some test technique. But there is no doubt, that risk stratification is crucial in patients with PH to guide further individual treatment decisions.

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