TAPSE/sPAP Predicts The Long-Term Prognosis in Pulmonary Arterial Hypertension Patients

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ABSTRACT

Introduction: Pulmonary arterial hypertension (PAH) is a progressive and life-threatening disease in which the risk stratification and the prognostic evaluation play a crucial role. Assessment of RV function is an important part of the follow-up. Tricuspid annular plane systolic excursion to systolic pulmonary artery pressure ratio (TAPSE/sPAP) is a simple, and readily available echocardiographic parameter which was stated as a prognostic predictor in various cardiac diseases. Herein, our aim was to evaluate the role of TAPSE/sPAP in prediction of long-term prognosis in PAH.

Patients and Methods: Our retrospective study enrolled a total of 41 PAH patients including 25 idiopathic PAH and 16 congenital heart disease associated PAH patients. Comprehensive echocardiographic examination, laboratory examination, six minutes walking test and cardiopulmonary exercise test were performed to all patients at the same day. Primary endpoint of the study was mortality or hospitalization. The relationship between TAPSE/sPAP and the composite outcomes were evaluated statistically.

Results: During mean 20.2 ± 9.2 months follow-up, nine patients were hospitalized, and three patients died. Median TAPSE/sPAP was 0.26 (0.19-0.40). TAPSE/sPAP [p= 0.003; HR (95% CI): 10.928 (2.240-53.316)] was found to be an independent predictor of composite outcomes in PAH patients. TAPSE/sPAP < 0.23 predicted mortality and hospitalization with a sensitivity of 80.0%, specificity of 71.4% [area under curve (AUC): 0.768; 95% CI: 0.596-0.939; p= 0.013]. The Kaplan-Meier cumulative survival curve revealed that as TAPSE/sPAP decreased, mortality and hospitalization rates increased significantly. Moreover, NT-proBNP [p= 0.014; HR (95% CI): 1.001 (1.000-1.001)] was found to be an independent predictor.

Conclusion: TAPSE/sPAP was an independent predictor of long-term prognosis in PAH. TAPSE/sPAP which is a simple, cheap and readily available echocardiographic parameter, might be used as an important prognostic factor in PAH patients.

Key Words: Prognosis; pulmonary arterial hypertension; TAPSE/sPAP.

TAPSE/sPAP Pulmoner Arteriyel Hipertansiyon Hastalarında Uzun Dönem Prognozu Öngördürür

ÖZ

Giriş: Pulmoner arteriyel hipertansiyon (PAH), risk sınıflandırmasının ve prognostik değerlendirmenin önemli rol oynadığı, ilerleyici ve yaşamı tehdit eden bir hastalıktır. Sağ ventrikül fonksiyonunun değerlendirilmesi, izlemin önemli bir parçasıdır. Triküspit anüler düzlem sistolik ekskürsiyonu/sistolik pulmoner arter basınç oranı (TAPSE/sPAP), çeşitli kardiyak hastalıklarda prognostik prediktör olarak belirtilen basit ve kolay ulaşılabilir bir ekokardiyografik parametredir. Bu çalışmada amaç, TAPSE/sPAP'ın PAH'ta uzun dönem prognozu öngörmedeki rolünü değerlendirmektir.

Hastalar ve Yöntem: Retrospektif çalışmaya, 25'i idiyopatik ve 16'sı doğumsal kalp hastalığı ile ilişkili PAH olmak üzere toplam 41 PAH hastası dahil edildi. Tüm hastalara aynı gün kapsamlı ekokardiyografik inceleme, laboratuvar incelemesi, altı dakika yürüme testi ve kardiyopulmoner egzersiz testi uygulandı. Çalışmanın birincil sonlanım noktası, ölüm veya hastaneye yatıştı. TAPSE/sPAP ile bileşik sonuçlar arasındaki ilişki istatistiksel olarak değerlendirildi.

Bulgular: Ortalama 20.2 ± 9.2 aylık takipte üç hastada mortalite, dokuz hastada hastaneye yatış gerçekleşmiştir. Medyan TAPSE/sPAP 0.26 (0.19-0.40) idi. TAPSE/sPAP [p= 0.003; HR (%95 CI): 10.928 (2.240-53.316)], PAH hastalarında bileşik sonuçların bağımsız bir prediktörü olarak bulunmuştur. TAPSE/sPAP < 0.23, %80.0 duyarlılık, %71.4 özgüllük ile mortalite ve hastaneye yatışı öngördürmekteydi [eğri altında kalan alan (EAA): 0.768; %95 CI: 0.596-0.939; p= 0.013]. Kaplan-Meier kümülatif sağkalım eğrisi, TAPSE/sPAP düştükçe mortalite ve hastaneye yatış oranlarının önemli ölçüde arttığını ortaya koymuştur. Ayrıca, NT-proBNP [p= 0.014; HR (%95 CI): 1.001 (1.000-1.001)] bağımsız prediktör olarak bulunmuştur.

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Sonuç: TAPSE/sPAP, PAH'ta uzun dönem prognozun bağımsız bir prediktörüdür. Basit, ucuz ve kolay ulaşılabilir bir ekokardiyografik parametre olan TAPSE/sPAP, PAH hastalarında önemli bir prog-nostik faktör olarak kullanılabilir.

Anahtar Kelimeler: Prognoz; pulmoner arteriyel hipertansiyon; TAPSE/sPAP.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive and life-threatening disease which is characterized with increased pulmonary arterial pressure and pulmonary vascular resistance. The current guidelines highlight the importance of risk stratification and prognostic evaluation in PAH patients' follow-up[1]. Right ventricular (RV) function is one of the most important determinants of symptoms and outcomes in PAH patients[2,3]. Although cardiac magnetic resonance is the gold standard modality in determining the function and the volume of RV, high costs and unavailability limit its daily use. Previous studied showed that 2-dimensional (2-D), 3-dimensional (3-D) speckle tracking echocardiography with or without 3-D RV construction are important imaging techniques to evaluate RV in patients with pulmonary hypertension[4-7]. However, the complexity of the techniques and expert requirement restrict their clinical use. Tricuspid annular plane systolic excursion to systolic pulmonary artery pressure ratio (TAPSE/sPAP) which is a simple, cheap, readily available echocardiographic parameter, was presented as non-invasive, indirect measurement of RV contractile function and RV-pulmonary arterial (PA) coupling[8-10]. In our study, we aimed to evaluate the utility of TAPSE/sPAP in prediction of long-term prognosis in PAH patients.

PATIENTS and METHODS

Study Population

Our study retrospectively included 41 PAH patients who admitted to our PH outpatient clinic between October 2018 and November 2020. The inclusion criteria were age ≥ 18 years old; diagnosis of PAH including IPAH and congenital heart disease associated PAH which was confirmed by right heart catheterization (RHC); stable clinical status under medical treatment. Exclusion criteria were PH patients other than IPAH and congenital heart disease associated PAH diagnosis, patients with unstable clinical status or hospitalized patients, inadequate image quality and missing data. Comprehensive echocardiographic examination, laboratory examination, 6 minutes walking test (6MWT) and cardiopulmonary exercise test (CPET) were performed to all patients at the same day. The relationship between TAPSE/sPAP and the prognosis of the patients were evaluated statistically. The study was conducted in accordance with the principles of the Helsinki Declaration and approved by the local Institutional Review Board. A written informed consent was obtained from all patients.

Echocardiographic Examination

All transthoracic echocardiographic (TTE) [Philips Epiq 7C (Philips Healthcare Andover, MA, USA) machine with an X5-1 transducer] examinations were performed by an experienced echocardiographer blinded to the patients' information in accordance with ASE/ESC guidelines[11]. Systolic pulmonary artery pressure (sPAP) was calculated from the peak tricuspid regurgitation (TR) jet velocity, using the simplified Bernoulli equation and addition of the estimated RA pressure (RAP). RAP was estimated from inferior vena cava (IVC) diameter and collapsibility. A normal IVC diameter (≤ 2.1 cm) and inspiratory collapse of > 50% suggests an estimated RAP of 3 mmHg (range, 0-5 mmHg); a normal IVC diameter without inspiratory collapse of > 50% and dilatation (> 2.1 cm) with inspiratory collapse (> 50%) suggests an estimated RAP of 8 mmHg (range, 5-10 mmHg); and dilatation (> 2.1 cm) without inspiratory collapse of > 50% suggests an estimated RAP of 15 mmHg[12].

RA area was measured just prior to tricuspid valve (TV) opening in the apical 4 chamber view (A4C), by tracing the RA blood-tissue interface, excluding the area under the TV annulus[11]. Right ventricular (RV) area was manually traced of RV endocardial border from the lateral TV annulus along the free wall to the apex and back to medial TV annulus, along the interventricular septum at end-diastole[11]. Left ventricular (LV) area was calculated with the similar manner. RV function was evaluated by tricuspid annular plane systolic excursion (TAPSE) and peak systolic velocity of tricuspid annulus (S'). TAPSE was acquired by placing an M-mode cursor through the TV annulus and measuring the amount of longitudinal motion of the annulus at peak systole[12]. S' was obtained from the apical approach by pulsed-wave DTI (cm/sec), sample volume was placed to the lateral corner of TV annulus and the peak annular systolic velocity was recorded[11]. TAPSE/sPAP was calculated as the ratio of TAPSE to sPAP. Left ventricular ejection fraction (LVEF) was measured from A4C view using the modified Simpson's biplane method[11].

Laboratory Examination

Venous blood samples were drawn into EDTA acid Vacutainer test tubes (Mediost BV, Doesburg, The Netherlands) prior to 6MWT and CPET. An electrochemiluminescence immunoassay (ProBNP Elecsys, Roche Diagnostics GmbH, Mannheim, Germany) was used for N-terminal prohormone of brain natriuretic peptide (NT-proBNP).

Six Minutes Walking Test (6MWT)

Before the test, patients rested for at least 10 minutes and medications were recorded. Before and after the test, heart rate, blood pressure, oxygen saturation and Borg scale score were recorded. 6 minutes walking distance (6MWD) was calculated[13].

Cardiopulmonary Exercise Test (CPET)

Patients with IPAH had a treadmill exercise ergospirometry test based on a Bruce protocol (Ergometrics 900, Ergoline, Bitz, Germany). Breath to-breath measurements of oxygen uptake (VO_2), carbon dioxide production (VCO_2), and ventilation (VE) values were analyzed. Heart rate, blood pressure and ventilation were recorded continuously during ergospirometry. We measured ventilatory flow, inspiratory and expiratory oxygen concentration difference, expiratory carbon dioxide concentration. From these variables oxygen uptake, peak oxygen uptake, carbon dioxide delivery, respiratory exchange ratio (RER) and ventilatory equivalents for oxygen and carbon dioxide (VE/VO_2, VE/VCO_2) were calculated by machine. Patients were encouraged to exercise to exhaustion or to a RER ≥ 1.0. VO_2 max was defined as the amount of oxygen consumed by the body at the peak of tolerable exercise. The anaerobic threshold (AT) was determined from the plot of carbon dioxide output (VCO_2) against oxygen uptake (VO_2), where the slope of this linear relation increased owing to a rise in VCO_2 (V-slope method). If no agreement was obtained, the AT was considered not identified. VE/VO_2 and VE/VCO_2 was defined as ventilator efficiency[14]. VE/VCO_2 slope was obtained by linear regression analysis of the relationship between VE and VCO_2 during exercise.

Study Endpoint

The primary endpoint of the study was mortality or hospitalization. The patients were divided into two groups according the presence of endpoint.

Statistical Analysis

Data was analyzed using the Statistical Package for the Social Sciences, version 24.0 (SPSS Inc., Chicago, Illinois, USA). Whether the variables show normal distribution; visual (histograms, probability curves) and analytical methods (Kolmogorov-Smirnov or Shapiro-Wilk) were evaluated. Numerical variables showing normal distribution were expressed as mean ± standard deviation (SD), numerical variables not showing normal distribution were expressed as median (interquartile range) and categorical variables as percentage (%). Numerical variables were evaluated using the Mann-Whitney U test between the two groups. Chi-Square or Fisher exact test were used to compare categorical variables. Receiver operating characteristic (ROC) curve was generated to investigate the prognostic accuracy of TAPSE/sPAP rate for composite outcome. Event-free survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Unadjusted and adjusted Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CI) for composite outcome. P value < 0.05 was considered statistically significant.

RESULTS

Our study enrolled 41 PAH patients including 25 IPAH and 16 congenital heart disease associated PAH patients. The mean age of the study population was 45.7 ± 17.3 and 15 of the patients were male. During a mean follow-up of 20.2 ± 9.2 months, nine patients were hospitalized, and three patients died. Four of the patients had positive vasoreactivity test, therefore they were under the calcium channel blocker therapy. Twenty two patients were under PAH-specific monotherapy, 20 of them were using endothelin receptor antagonists (ERA) and two were under phosphodiesterase 5 (PDE5) inhibitor treatment. Fifteen patients were under PAH-specific combination therapy, 14 of them were using ERA + PDE5 inhibitors and one was under ERA + PDE5 inhibitors + prostacyclin analogue treatment.

Study population was divided into two groups according to the presence of primary endpoint as composite outcome (+) and composite outcome (-) groups. There wasn't any significant difference between two groups in terms of demographic features except age and hypertension. Composite outcome (+) group was older (p= 0.045) and more hypertensive (p= 0.045). NT-proBNP levels (p= 0.004), RA area (p= 0.037) and sPAP (p= 0.006) were significantly higher, TAPSE (p= 0.036), TAPSE/sPAP (p= 0.013) and S' (p= 0.024) were significantly lower in composite outcome (+) group. Other clinical, echocardiographic and exercise parameters were not significantly different between two groups (Table 1).

Median TAPSE/sPAP of the study population was 0.26 (0.19-0.40) and composite outcome (+) group had significantly lower TAPSE/sPAP [composite outcome (-): 0.30 (0.20-0.49) vs. composite outcome (+): 0.20 (0.13-0.24), p= 0.013] (Figure 1). ROC analysis was generated to detect the optimal cut-off value of TAPSE/sPAP in predicting mortality and hospitalization (Figure 2). TAPSE/sPAP < 0.23 predicted mortality and hospitalization with a sensitivity of 80.0%, specificity of 71.4%, positive predictive value of 50.0%, negative predictive value of 90.9% and accuracy of 73.7% [area under curve (AUC): 0.768; 95% CI: 0.596-0.939; p= 0.013]. The Kaplan-Meier cumulative survival curve was generated with this cut-off value which revealed that as TAPSE/sPAP decreased, mortality and hospitalization rates increased significantly (Figure 3).

Table 1. Basal demographic, clinical, echocardiographic and laboratory features of study population

	Total (n= 41)	Composite outcome (-) (n= 29)	Composite outcome (+) (n= 12)	p value
Age	45.7 ± 17.3	42.5 ± 17.0	53.7 ± 16.1	**0.045**
Gender (male), n (%)	15 (36.6%)	11 (37.9%)	4 (33.3%)	1.0
DM, n (%)	4 (9.8%)	2 (6.9%)	2 (16.7%)	0.567
HT, n (%)	17 (41.5%)	9 (31.0%)	8 (66.7%)	**0.045**
CRF, n (%)	4 (9.8%)	1 (3.4%)	3 (25.0%)	0.068
COPD, n (%)	10 (24.4%)	6 (20.7%)	4 (33.3%)	0.441
6 MWD (m)	405 (270-523)	450 (293-533)	337 (225-480)	0.206
Peak VO_2 (mL/min/kg)	13.0 (9.5-16.2)	14.1 (9.9-16.1)	10.7 (7.4-16.2)	0.309
NT-proBNP (pg/mL)	202 (128-1060)	176 (101-442)	1223 (375-1970)	**0.004**
LVEF (%)	55 (55-60)	55 (55-60)	55 (53-60)	0.547
RA area (cm^2)	21.0 ± 6.9	19.8 ± 6.2	24.2 ± 7.7	**0.037**
RVED area (cm^2)	24.2 ± 6.7	24.0 ± 5.9	24.8 ± 8.9	0.716
LVED area (cm^2)	22.9 ± 7.4	23.8 ± 7.9	20.4 ± 5.2	0.385
TAPSE (mm)	19.7±5.6	20.6±5.7	17.0±4.7	**0.036**
sPAP (mmHg)	73.9±26.5	66.3±23.7	91.8±24.6	**0.006**
TAPSE/sPAP (mm/mmHg)	0.26 (0.19-0.40)	0.30 (0.20-0.49)	0.20 (0.13-0.24)	**0.013**
S' (cm/s)	11.9 ± 2.9	12.6 ± 2.8	10.2 ± 2.2	**0.024**
Diagnosis				0.504
IPAH	25 (61.0%)	16 (55.2%)	9 (75.0%)	
CHD associated				
PDA	2 (4.9%)	2 (6.9%)	0 (0.0%)	
ASD	2 (4.9%)	1 (3.4%)	1 (8.3%)	
Operated ASD	4 (9.8%)	4 (13.8%)	0 (0.0%)	
VSD	6 (14.6%)	4 (13.8%)	2 (16.7%)	
Operated VSD	2 (4.9%)	2 (6.9%)	0 (0.0%)	
Functional class				0.149
1	20 (54.1%)	17 (65%)	3 (27.3%)	
2	4 (10.8%)	2 (7.7%)	2 (18.2%)	
3	10 (27.0%)	6 (23.1%)	4 (36.4%)	
4	3 (8.1%)	1 (3.8%)	2 (18.2%)	

Data are presented as percentage, mean ± standard deviation or median (interquartile range).
ASD: Atrial septal defect, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal fail-ure, DM: Diabetes mellitus, HT: Hypertension, IPAH: Idiopathic pulmonary arterial hypertension, LVED: Left ventricular end-diastolic, LVEF: Left ventricular ejection fraction, NT-proBNP: N-terminal pro-hormone of brain natriuretic peptide, PDA: Patent ductus arteriosus, RA: Right atrium, RVED: Right ventricular end-diastolic, S': Tricuspid annular peak systolic velocity, sPAP: Systolic pulmonary arterial pressure, TAPSE: Tricuspid annular plane systolic excursion, VO_2: Oxygen up-take, VSD: Ventricular septal defect, 6MWD: 6 minutes walking distance.

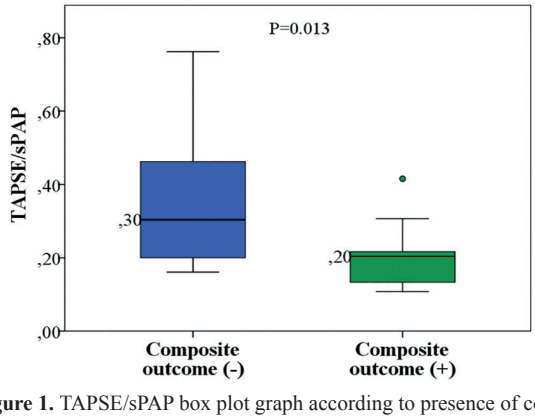


Figure 1. TAPSE/sPAP box plot graph according to presence of composite outcomes in PAH patients.

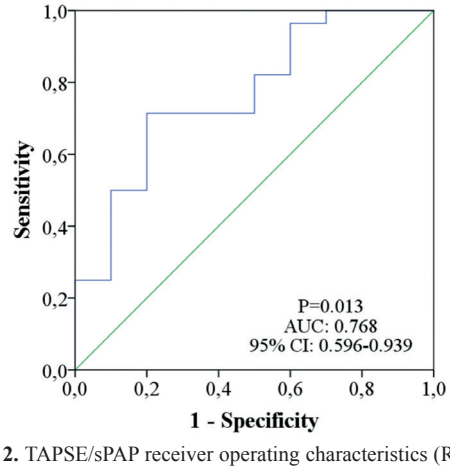


Figure 2. TAPSE/sPAP receiver operating characteristics (ROC) curve for prediction of composite outcomes in PAH patients. AUC: area under curve.

Table 2. Univariate and multivariate Cox-proportional hazard analysis for prediction of composite out-comes in PAH patients

	Unadjusted		Age-adjusted	
	HR (95% CI)	p	HR (95% CI)	p
TAPSE/sPAP < 0.23	8.664 (1.826-41.117)	**0.007**	10.928 (2.240-53.316)	**0.003**
Peak VO_2	0.880 (0.752-1.030)	0.110	0.908 (0.770-1.070)	0.250
6 MWD	0.996 (0.993-1.000)	0.075	0.999 (0.994-1.004)	0.572
NT-proBNP	1.001 (1.000-1.001)	**0.001**	1.001 (1.000-1.001)	**0.014**
RA area	1.087 (1.001-1.180)	**0.047**	1.077 (0.979-1.185)	0.129
Functional class	1.931 (1.105-3.376)	**0.021**	1.540 (0.754-3.148)	0.236

HR: Hazard ratio, CI: Confidence interval, other abbreviations as in Table 1.

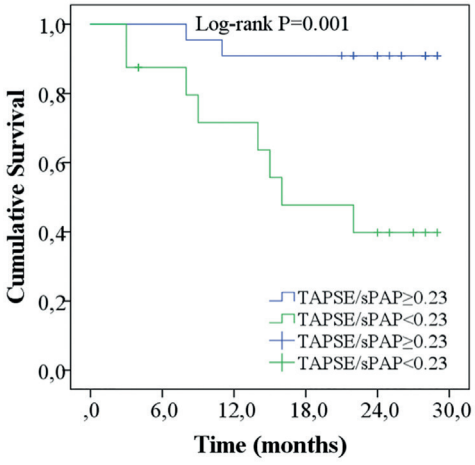


Figure 3. The Kaplan-Meier cumulative survival curve for composite out-comes.

On the other hand for the investigation of TAPSE/sPAP effect over composite outcomes, univariate and multivariate Cox-proportional hazard analysis were performed and the results were summarized in Table 2. Univariate Cox-proportional hazard analysis revealed that TAPSE/sPAP (p= 0.007) was a potential risk factor for composite outcomes. Additionally, NT-proBNP (p= 0.001), RA area (p= 0.047) and functional class (p= 0.021) were found to be associated with composite outcomes. Even after the adjustment for age, TAPSE/sPAP [p= 0.003; HR (95% CI): 10.928 (2.240-53.316)] and NT-proBNP [p= 0.014; HR (95% CI): 1.001 (1.000-1.001)] were found to be independent predictors of composite outcomes in PAH patients.

DISCUSSION

In present study, we investigated the utility of TAPSE/sPAP in prediction of long-term mortality or hospitalization in PAH patients. Our study revealed; I) TAPSE/sPAP was an independent predictor of long-term prognosis in PAH patients. II) TAPSE/sPAP < 0.23 predicted mortality and hospitalization with a sensitivity of 80.0%, specificity of 71.4% and as TAPSE/sPAP decreased, mortality and hospitalization rates increased significantly. III) Moreover, NT-proBNP was found to be an independent predictor.

PAH is a progressive disease in which the risk stratification and the prognostic evaluation compose the backbone of the patient management. The latest guideline and three registries which were released after the guideline highlighted the importance of frequent risk assessment and achieving the low risk status[1,15-17]. The easier the parameters used, the more applicable it will be in daily life. Therefore, in our study, for prognostic evaluation, we chose a simple, readily available parameter, such as TAPSE/sPAP, that every echocardiographer can easily calculate. TAPSE/sPAP was researched in different patient groups such as heart failure patients, patients who underwent CRT or TAVI, patients with moderate to severe tricuspid regurgitation, patients with acute respiratory distress syndrome[8,18-22]. All these studies revealed the prognostic power of TAPSE/sPAP. To the best of our knowledge, the prognostic value of TAPSE/sPAP in PAH patients was just researched by Tello et al.[23]. Their study population was heterogeneous by including patients with IPAH, heritable PAH, HIV associated PAH, congenital heart disease associated PAH, portopulmonary hypertension, pulmonary venoocclusive disease with severely compromised pulmonary hemodynamics, and impaired functional status. Our study differs from their study in term of study population, we just included IPAH and congenital heart disease associated PAH patients and the majority of our patients had better functional class and hemodynamic status. Moreover, the two studies were also different from each other in term of endpoints, their study's endpoint was overall mortality, however ours endpoint was mortality or hospitalization. Although there were major differences between the study population and the design of the studies, our study confirmed their findings and revealed that TAPSE/sPAP was an independent predictor of long-term prognosis in PAH. NT-proBNP is a well-known prognostic parameter which has place in current guideline[1]. We also found that NT-proBNP was an independent predictor of long-term mortality and hospitalization in PAH patients, compatible with the literature.

LIMITATIONS

The present study had some limitations. First, our study had a retrospective design and a relatively small number of the study population. Second, TAPSE reflects longitudinal shortening of the RV. During RV impairment, TAPSE reaches a minimum value and shows no further decrease[24]. The reliability of TAPSE as a parameter of RV function may thus be reduced in the advanced stages of RV failure. Third, other parameters representing RV function, such as FAC or global longitudinal strain, have not been investigated in our study.

CONCLUSION

In present study, we found that TAPSE/sPAP was an independent predictor of long-term hospitalization or mortality in PAH patients. Therefore, TAPSE/sPAP which is a simple, cheap and readily available echocardiographic parameter, might be used as an important prognostic factor in PAH patients.

Ethics Committee Approval: This study was approved by Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Ethics Committee (2021/22, Date: 23.03.2021).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - BU, MY, AD, AG; Analysis/Interpretation - BU, AD, SK, KS; Data Collection - KS, AU, HA, SK; Writing - BU; Critical Revision - MY, OC, ME; Statistical Analysis - AD, BU, AG; Overall Responsibility - BU; Final Approval - All of authors.

Conflict of Interest: The authors have no conflicts of interest to declare.

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