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ORIGINAL ARTICLE / ÖZGÜN MAKALE

The prognostic value of the TAPSE/PASP ratio in lung transplant candidates

Akciğer nakli adaylarında TAPSE/PASP oranının prognostik değeri

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ABSTRACT

Background: In this study, we aimed to investigate the prognostic value of the tricuspid annular systolic excursion/pulmonary arterial systolic pressure (TAPSE/PASP) ratio as a marker of right ventricle-pulmonary artery uncoupling in patients listed for lung transplantation.

Methods: Between January 2011 and December 2020, a total of 173 patients (114 males, 59 females; mean age: 53.1±12.5 years; range, 18 to 77 years) who had advanced lung disease or pulmonary vascular disease and were included in the lung transplant list were retrospectively analyzed. Demographic characteristics, laboratory values, long-term mortality data, and clinical and cardiac catheterization data of the patients were compared using a TAPSE/PASP cut-off value of 0.55 mm/mmHg. The univariate and multivariate regression analyses were performed to identify the value of TAPSE/PASP ratio in predicting long-term mortality. The maximal selective rank test was carried out to determine the optimal cut-off value for TAPSE/PASP ratio.

Results: The univariate regression analysis revealed that the TAPSE/PASP ratio, six-minute walk distance, and albumin level were found to be predictors of mortality (hazard ratio [HR]=0.61, 95% confidence interval [CI]: 0.46-0.80, p=0.007; HR=0.72, 95% CI: 0.56-0.91, p=0.007; and HR=0.77, 95% CI: 0.59-0.99, p=0.04, respectively). In the multivariate regression analysis, the TAPSE/PASP ratio, body mass index, and six-minute walk distance were the predictors of mortality (HR=0.49, 95% CI: 0.34-0.70, p=0.004; HR=0.71, 95% CI: 0.51-0.97, p=0.03; and HR=0.71, 95% CI: 0.54-0.94, p=0.01, respectively).Through the maximal selective rank test, the optimal threshold value for TAPSE/PASP ratio was found to be 0.29 mm/mmHg. Patients with TAPSE/PASP >0.29 mm/mmHg had an average life expectancy of 47.8 months, while the patients with TAPSE/PASP <0.29 mm/mmHg had an average life expectancy of 17.2 months.

Conclusion: Our study results suggest that a TAPSE/PASP ratio of <0.29 mm/mmHg is a poor prognostic factor for long-term mortality in patients on the waiting list for lung transplantation.

Keywords: Echocardiography, lung transplantation, right ventricle-pulmonary artery uncoupling, TAPSE/PASP ratio.

ÖZ

Amaç: Bu çalışmada, akciğer nakil listesinde olan hastalarda triküspit anüler sistolik ekskürsiyon/pulmoner arter sistolik basıncı (TAPSE/PASP) oranının sağ ventrikül-pulmoner arter ayrılmasının bir belirteci olarak prognostik değeri araştırıldı.

Çalışma planı: Ocak 2011-Aralık 2020 tarihleri arasında ileri evre akciğer hastalığı veya pulmoner vasküler hastalığı olan ve akciğer nakil listesine eklenen toplam 173 hasta (114 erkek, 59 kadın; ort. yaş: 53.1±12.5 yıl; dağılım, 18-77 yıl) retrospektif olarak incelendi. Hastaların demografik özellikleri, laboratuvar değerleri, uzun dönem mortalite verileri ve klinik ve kardiyak kateterizasyon verileri 0.55 mm/mmHg TAPSE/PASP eşik değeri kullanılarak karşılaştırıldı. TAPSE/PASP oranının uzun dönem mortaliteyi öngörmedeki değerini belirlemek amacıyla tek değişkenli ve çok değişkenli regresyon analizleri yapıldı. TAPSE/PASP oranı için optimal eşik değerini belirlemek amacıyla maksimum seçici sıra testi uygulandı.

Bulgular: Tek değişkenli regresyon analizinde TAPSE/PASP oranı, 6 dakika yürüme mesafesi ve albümin düzeyi mortalitenin öngördürücüleri olarak bulundu (sırasıyla risk oranı [HR]=0.61, 95% güven aralığı [GA]: 0.46-0.80, p=0.007; HR=0.72, 95% GA: 0.56-0.91, p=0.007 ve HR=0.77, 95% GA: 0.59-0.99, p=0.04). Çok değişkenli analizde TAPSE/PASP oranı, vücut kütle indeksi ve 6 dakikalık yürüme mesafesi mortalitenin öngördürücüleri idi (sırasıyla HR=0.49, 95% GA: 0.34-0.70, p=0.004; HR=0.71, 95% GA: 0.51-0.97, p=0.03 ve HR=0.71, 95% GA: 0.54-0.94, p=0.01). Maksimal seçici sıra testi ile TAPSE/PASP oranı için optimal eşik değeri 0.29 mm/mmHg olarak bulundu. TAPSE/PASP >0.29 mm/mmHg olan hastaların ortalama yaşam beklentisi 47.8 ay iken, TAPSE/PASP <0.29 mm/mmHg olan hastaların ortalama yaşam beklentisi 17.2 ay idi.

Sonuç: Çalışma sonuçlarımız <0.29 mm/mmHg'lik TAPSE/PASP oranının akciğer nakli için bekleme listesinde olan hastalarda uzun dönem mortalitenin kötü bir prognostik faktörü olduğunu göstermektedir.

Anahtar sözcükler: Ekokardiyografi, akciğer nakli, sağ ventrikül-pulmoner arter ayrılması, TAPSE/PASP oranı.

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In recent years, lung transplantation (LTx) has been recognized as a preferred option in the treatment of advanced lung parenchymal diseases and pulmonary vascular diseases.[1,2] Lung transplantation may offer significant advantages in terms of long-term survival outcomes, particularly in treatment-refractory conditions such as emphysema, cystic fibrosis (CF), pulmonary fibrosis, pulmonary arterial hypertension (PAH), bronchiectasis, sarcoidosis, and connective tissue diseases. Many patients on the transplant list die during waiting time due to lack of donor organs. Therefore, it is extremely important to evaluate the prognosis of patients based on clinical status, laboratory and imaging methods and to obtain predictive information about the course of the disease to determine the priority and timing of LTx.[3]

Pulmonary hypertension (PH) has been reported to have an effect on mortality in LTx candidates and also in heart, kidney, and liver transplant patients.[4-6] Whether or not PH develops is also important in terms of the treatment plan in LTx candidates, the need for unilateral or bilateral LTx, and the need for extracorporeal membrane oxygenator (ECMO) during the operation.[7] During the LTx evaluation process, evaluation of the candidate by cardiac catheterization, determination of the presence of PH by calculating pulmonary artery systolic pressure (PASP) and mean pulmonary artery pressure (mPAP) is a routine and gold-standard method in terms of progression of the patient's underlying lung disease and correct timing for transplantation. Secondary to PH, the right ventricle (RV) tries to maintain RV-pulmonary artery (PA) coupling and flow by increasing contractility in response to increased afterload. However, if this compliance is exhausted and the RV is insufficient, an increase in RV filling pressures, RV dilatation and systemic congestion may occur due to different mechanisms such as Starling's law.[8-10] The function of RV is one of the main determinants of prognosis in patients with severe PAH and PH secondary to advanced pulmonary disease.[8,9] Tricuspid annular plane systolic motion (TAPSE) is a critical echocardiographic parameter reflecting RV function that may be useful in LTx candidate evaluation, but the gold-standard measure of RV contractility is end-systolic elastance (Ees) derived from pressure-volume loops by cardiac catheterization. The RV-PA coupling is best characterized by the ratio of RV Ees to arterial elastance (Ea).[8-10] The TAPSE/PASP ratio is thought to be a non-invasive, echocardiographic marker of RV-PA coupling. In addition, the prognostic importance of the TAPSE/PASP ratio in various diseases such as PAH and congestive heart failure has been demonstrated by previous studies.[12-21]

In the present study, we aimed to evaluate the prognostic value of the TAPSE/PASP ratio in patients listed for LTx.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Koşuyolu Yüksek İhtisas Training and Research Hospital, Department of Cardiology between January 2011 and December 2020. A total of 331 patients who were admitted to our clinic for advanced lung disease or pulmonary vascular disease and who were evaluated by the Lung Transplant Council according to the International Society for Heart and Lung Transplantation (ISHLT) criteria and included in the transplant list were evaluated. Demographic characteristics, laboratory values, spirometry measurements, six-minute walk distance (6MWD) values, echocardiography findings, and cardiac catheterization results of patients were prospectively obtained. Retrospective analysis of prospectively gathered data was made from the hospital database. Among these patients, 146 were not included in the study, as they underwent LTx during the follow-up period. Approximately 12 patients were not included in the study due to lack of data or inaccessibility of data. The remaining 173 patients (114 males, 59 females; mean age: 53.1±12.5 years; range, 18 to 77 years) were recruited for the study (Figure 1). A written informed consent was obtained from each patient. The study protocol was approved by the Koşuyolu Yüksek İhtisas Training and Research Hospital Ethics Committee (date: 04/07/2023, no: 2023/11/706). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Echocardiographic examinations of patients were performed with a 3.5-MHz or M5S ultrasound probe and Vivid E95 ultrasound device (General Electric Vingmed Ultrasound, Milwaukee, WI, USA). All standard measurements were made in accordance with the European Association of Cardiovascular Imaging (EACVI) and American Society of Echocardiography (ASE) guidelines.[22] The echocardiographic parameters were as follows: left ventricular (LV) end-diastolic and end-systolic diameters with M-mode, LV ejection fraction (LVEF%) calculated by the Biplane Simpson's method, TAPSE, the maximum jet velocities (V_{max}) calculated from the tricuspid regurgitant jet, and

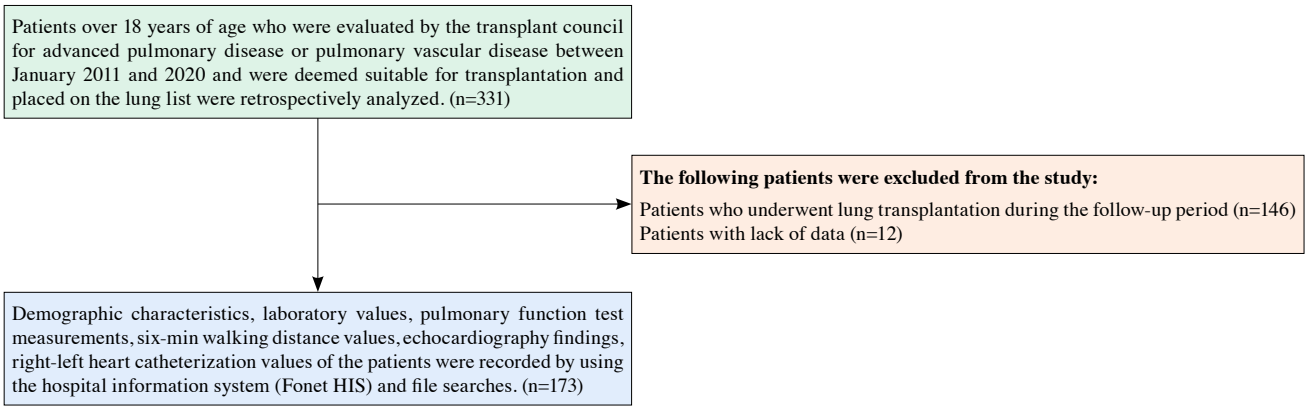

Figure 1. Study flowchart.

pulmonary artery systolic pressure calculation by Bernoulli equation in accordance with currently available echocardiography guidelines.[22] Cardiac catheterization was performed via the femoral artery and vein in all patients. Right ventricular, right atrial, PA, aortic, and LV pressures, and blood gas analysis from these cavities were obtained. Cardiac output, cardiac index, pulmonary vascular resistance (PVR), and systemic vascular resistance were calculated using the Fick method.

In previous studies, different cut-off values such as 0.31 mm/mmHg and 0.47 mm/mmHg were used for the TAPSE/PASP ratio.[18,23] Patients included in the study were divided into two groups according to TAPSE/PASP ratio with a cut-off value of 0.55 mm/mmHg. This cut-off value was considered the cut-off value for the prediction of PH in the 2022 European Society of Cardiology (ESC) PH guideline.[24] In Group 1, there were 64 patients with a TAPSE/PASP ratio of >0.55 mm/mmHg, while in Group 2, there were 109 patients with a TAPSE/PASP ratio of <0.55 mm/mmHg. Comparison between these groups was made regarding demographic characteristics, comorbidities, laboratory values, long-term mortality and cardiac catheterization data.

Statistical analysis

Statistical analysis was performed using the Jamovi version 2.6.2 (The Jamovi project, Sydney, Australia). Distribution of the variables was checked using the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed in mean ± standard deviation (SD) and non-normally distributed continuous variables were expressed in median and interquartile range (IQR). Categorical variables were expressed in number and frequency. Numerical values between the two groups were compared using Student t-test or Mann-Whitney U test according to whether they were normally distributed or not, and categorical variables were compared using the chi-square or Fisher exact test. The Cox proportional regression analysis was used to test the parameters that may be clinically important for disease prognosis and mortality by univariate and multivariate analysis. Linear model analysis of variance (ANOVA) test was performed to compare the mean distributions and *p* values of echocardiography and cardiac catheterization data between the groups. The maximal selected rank test was used to determine optimal cut-off value for TAPSE/PASP ratio. The survival analysis using Kaplan-Meier curves was carried out for both groups, which were divided according to the optimal cut-off value. A *p* value of <0.05 was considered statistically significant.

RESULTS

There was no significant difference in the sex distribution and mean age between the groups (p=0.78 and p=0.55, respectively). In addition, both groups were comparable regarding body mass index (BMI), follow-up duration, presence of diabetes, hypertension and coronary artery disease (p=0.93, p=0.21, p=0.11, p=0.72, and p=0.54, respectively). Although the mean brain-type natriuretic peptide values were higher in Group 2, this difference did not reach statistical significance (103.2±174.2 *vs.* 60.3±68.7, p=0.06). Long-term mortality was higher in the lower TAPSE/PASP group (65.1% *vs.* 43.8%, p=0.006). Comparisons between these two groups are given in Table 1.

Table 1. Distribution of demographic data, blood parameters, echocardiographic parameters, cardiac catheterization data and long-term mortality according to TAPSE/PASP categories

	TAPSE/PASP ratio >0.55 (n=64)			TAPSE/PASP ratio <0.55 (n=109)			Number of total patients (n=173)			
Variables	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			53.9±11.3			52.7±13.3			53.1±12.5	0.55
Sex										0.78
Female	21	32.8		38	34.9		59	34.1		
Male	43	67.2		75	65.1		114	65.9		
BMI (kg/m^2)			23.1±3.9			23.2±4.4			23.2±4.2	0.93
Follow-up period (month)			38.6±34.4			32.4±29.7			34.7±31.6	0.21
Patient group										0.42
Interstitial lung disease	33	51.6		53	48.6		86	49.7		
Obstructive lung disease	17	26.6		26	23.9		43	24.9		
Infective lung disease	13	20.3		22	20.2		35	20.2		
Pulmonary vascular disease	1	1.6		8	7.3		9	5.2		
Diabetes mellitus	23	35.9		27	24.8		50	28.9		0.11
Hypertension	24	37.5		38	34.9		62	35.8		0.72
Coronary artery disease	10	15.6		21	19.3		31	17.9		0.54
NYHA classification										0.56
I	6	9.4		18	16.5		24	13.9		
II	23	35.9		39	35.8		62	35.8		
III	22	34.4		35	32.1		57	32.9		
IV	13	20.3		17	15.6		30	17.3		
Creatinine (mg/dL)			0.6±0.2			0.7±0.3			0.7±0.2	0.45
Hemoglobin (g/dL)			13.1±1.6			13±2.0			13±1.9	0.71
Albumin (g/dL)			3.8±0.6			3.7±0.6			3.8±0.6	0.39
Total bilirubin (mg/dL)			0.6±0.4			0.7±0.9			0.7±0.8	0.22
BNP (pg/mL)			60.3±68.7			103.2±174.2			87.3±145.7	0.06
Total cholesterol (mg/dL)			190±60.7			182.9±56.0			185.5±57.7	0.43
Long-term mortality	28	43.8		71	65.15		99	57.2		0.006

TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary artery systolic pressure; SD: Standard deviation; BMI: Body mass index; NYHA: New York Hearth Association classification, BNP: Brain-type natriuretic peptide.

In the linear model analysis, PVR, PA, right atrial, and LV end-diastolic pressures were found to be higher in the low TAPSE/PASP group (Supplementary Table 1). In addition, the distribution of spirometry and 6MWD data were evaluated according to TAPSE/PASP categories and no significant difference was found between the two groups (Supplementary Table 2).

Maximal selective rank test was performed to determine the optimal cut-off value of TAPSE/PASP ratio for long-term mortality. The optimal cut-off value for mortality was 0.29 mm/mmHg (Figure 2). Then, the patients were further divided into two groups as TAPSE/PASP <0.29 mm/mmHg and TAPSE/PASP >0.29 mm/mmHg. The average life expectancy was found to be higher in patients with TAPSE/PASP >0.29 mm/mmHg. Patients with TAPSE/PASP >0.29 mm/mmHg had 47.2 months average life expectancy, while patients with TAPSE/PASP <0.29 months had only 17.2 months average life expectancy. In patients with TAPSE/PASP >0.29 mm/mmHg, the survival rates at 12, 36, and 60 months were 80.1%, 56.5%, and 46.7%, respectively. In the group with TAPSE/PASP <0.29 mm/mmHg, the survival rates were 52.2%, 26.6%, and 14.3%, respectively (Supplementary Table 3). The higher survival for patients with higher TAPSE/PASP

ratio for a cut-off value of 0.29 mm/mmHg is demonstrated with Kaplan-Meier survival curves in Figure 3. Relative effect scheme of TAPSE/PASP ratio for long-term mortality is given in Figure 4.

Univariate regression analysis was performed for long-term mortality in patients on the waiting list for LTx. The TAPSE/PASP ratio, 6MWD, and albumin value were found to be predictors of

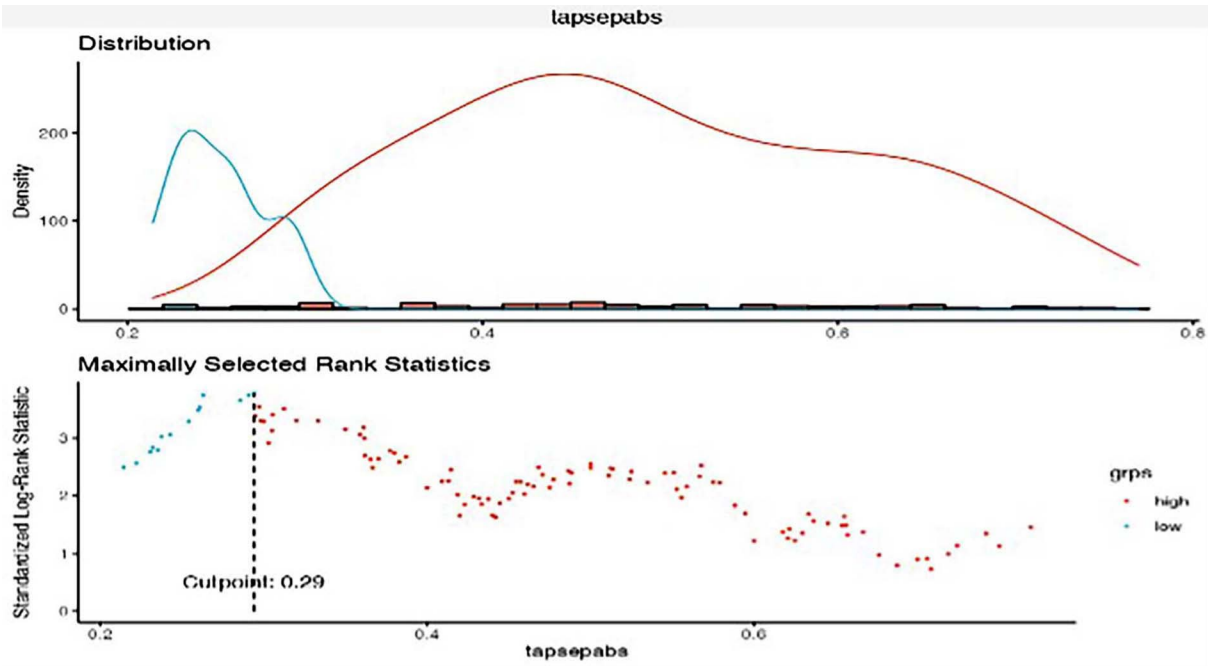

Figure 2. Optimal limit value determined by maximal selective rank test and distribution density of patients according to TAPSE/PASP value.

TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary artery systolic pressure.

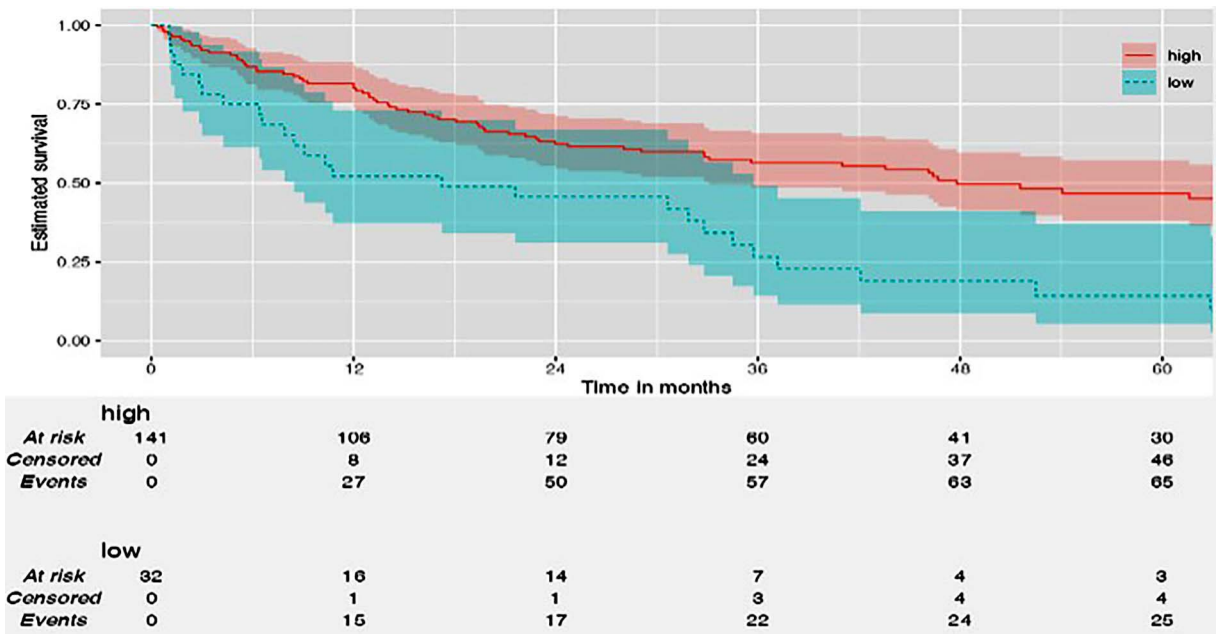

Figure 3. Kaplan-Meier plot for low and high TAPSE/PASP ratio groups for a cut-off value of 0.29 mm/mmHg.

TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary artery systolic pressure.

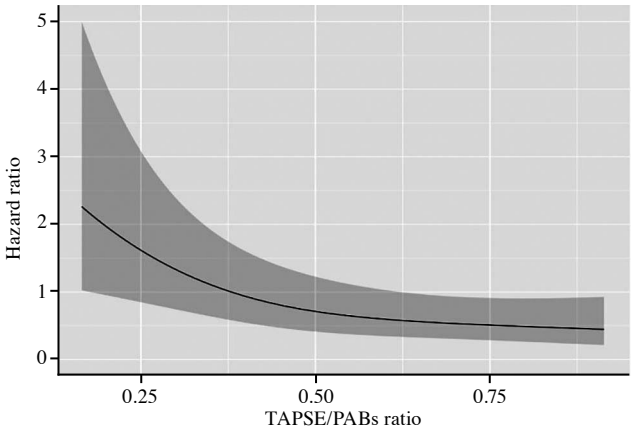

Figure 4. Relative effect scheme of TAPSE/PASP ratio for long-term mortality.

TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary artery systolic pressure.

mortality (hazard ratio [HR]=0.61, 95% confidence interval [CI]: 0.46-0.80, p=0.007; HR=0.72, 95% CI: 0.56-0.91, p=0.007; and HR=0.77, 95% CI: 0.59-0.99, p=0.04, respectively) (Table 3). In addition, multivariate regression analysis was carried out for long-term mortality. Accordingly, the TAPSE/PASP ratio, BMI, and 6MWD were found to be predictors of mortality (HR=0.49, 95% CI: 0.34-0.70, p=0.004; HR=0.71, 95% CI: 0.51-0.97, p=0.03; and HR=0.71, 95% CI: 0.54-0.94, p=0.01, respectively) (Table 4).

DISCUSSION

Lung transplantation is a treatment option which can provide significant advantages in advanced stage lung patients who do not respond to treatment such as chronic obstructive pulmonary disease (COPD), CF, idiopathic pulmonary fibrosis (IPF),

Table 2. Number of deaths and life expectancy according to the TAPSE/PASP ratio cut-off value of 0.29 mm/mmHg

Group	Number of patients	Death	Average life expectancy (months)	95% CI
TAPSE/PASP >0.29 mm/mmHg	141	71	47.8	33.1-88.6
TAPSE/PASP <0.29 mm/mmHg	32	28	17.2	8.47-35.7

TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary artery systolic pressure; CI: Confidence interval.

Table 3. Univariate COX regression analysis for long-term mortality in patients on the lung transplantation waiting list

Variables	HR	CI	*p*
Age (from 46 to 61 years)	0.97	0.77-1.22	0.82
TAPSE/PASP ratio (from 0.33 mmHg to 0.62 mm/mmHg)	0.61	0.46-0.80	0.007
Sex (female)	1.07	0.71-1.61	0.75
BMI (from 20 kg/m^2 to 26 kg/m^2)	0.79	0.60-1.06	0.11
Obstructive pulmonary disease *vs*. interstitial lung disease	0.68	0.42-1.11	0.123
Infective lung disease *vs*. interstitial lung disease	0.61	0.36-1.04	0.07
Pulmonary vascular disease *vs*. interstitial lung disease	0.76	0.30-1.89	0.55
PVR (from 2 WU to 4.7 WU)	1.08	0.89-1.29	0.42
BNP (from 29 pg/mL to 81 pg/mL)	1.02	0.97-1.08	0.43
FEV1/FVC (from 65% to 96%)	0.98	0.76-1.28	0.91
FEV1 (from 28% to 50%)	0.92	0.65-1.29	0.63
FVC (from 32% to 51%)	1.01	0.76-1.36	0.92
6MWD (from 250 m to 367 m)	0.72	0.56-0.91	0.007
Hemoglobin (from 11.9 g/dL to 14.3 g/dL)	1.03	0.79-1.33	0.83
Albumin (from 3.4 g/dL to 4.1 g/dL)	0.77	0.59-0.99	0.04
Total cholesterol (from 145 mg/dL to 218 mg/dL)	1.20	0.93-1.56	0.15

HR: Hazard ratio; CI: Confidence interval; TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary artery systolic pressure; BMI: Body mass index; PVR: Pulmonary vascular resistance; WU: Wood units; BNP: Brain-type natriuretic peptide; FEV1: Forced expiratory volume in 1st second; FVC: Forced vital capacity; 6MWD: Six-minute walk distance.

Table 4. Multivariate cox regression analysis for mortality in patients on the lung transplant waiting list

Variables	HR	CI	*p*
Age (46 to 61 years)	0.79	0.59-1.05	0.10
TAPSE/PASP (0.33 mmHg to 0.62 mm/mmHg)	0.49	0.34-0.70	0.004
Sex (female reference)	1.14	0.72-1.82	0.56
BMI (from 20 kg/m^2 to 26 kg/m^2)	0.71	0.51-0.97	0.03
Obstructive pulmonary disease *vs*. interstitial lung disease	0.66	0.40-1.09	0.11
Infective lung disease *vs*. interstitial lung disease	0.56	0.26-0.84	0.01
Pulmonary vascular disease *vs*. interstitial lung disease	0.60	0.23-1.60	0.30
PVR (2 WU to 4.7 WU)	0.78	0.59-1.01	0.06
BNP (from 29 pg/mL to 81 pg/mL)	1.02	0.96-1.10	0.45
FEV1/FVC (65% to 96%)	1.04	0.78-1.38	0.76
6MWD (250 m to 367 m)	0.71	0.54-0.94	0.01
Hemoglobin (from 11.9 g/dL to 14.3 g/dL)	1.18	0.88-1.59	0.25
Albumin (from 3.4 g/dL to 4.1 g/dL)	0.75	0.55-1.04	0.08
Total cholesterol (from 145 mg/dL to 218 mg/dL)	1.30	0.94-1.80	0.10

HR: Hazard ratio; CI: Confidence interval; TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary artery systolic pressure; BMI: Body mass index; PVR: Pulmonary vascular resistance; WU: Wood units; BNP: Brain-type natriuretic peptide; FEV1: Forced expiratory volume in 1st second; FVC: Forced vital capacity; 6MWD: Six-minute walk distance.

PAH, bronchiectasis, sarcoidosis, and connective tissue diseases.[3] As it is well-known, patients with advanced lung disease tend to develop additional comorbidities over time with the progression of lung disease. Some of these comorbidities include vasoconstriction of pulmonary vessels and hypertrophy of smooth muscle cells due to low alveolar oxygen pressure and hypoxia, leading to an increase in PAP pressures and PVR values.[25] In previous studies, even the secondary development of mild PH (PVR <5) in pulmonary patients adversely affects symptoms, hospitalization, and mortality.[26,27] In patients with severe PH, it has been associated with increased mortality even compared to patients with mild PH.[28,29]

Secondary PH in advanced lung disease increases the afterload and causes a pressure load on the RV. In the early period, the RV responds and adapts to this increased afterload by increasing its contractility and wall thickness to reduce wall tension according to Laplace's law. Thanks to this adaptation, the RV pumps sufficient blood to the PA despite the increased afterload and this is referred to as RV-PA coupling.[8,9] However, with the progression of the disease, this adaptation is impaired, RV systolic function cannot be increased further, a mismatch between myocardial oxygen demand and supply develops due to RV hypertrophy and increased filling pressure, RV failure develops and the coupling between RV-PA is disrupted.[30-32] In previous studies, development of RV dysfunction in advanced pulmonary patients such as COPD, interstitial lung disease (ILD) and CF has been associated with poor prognosis.[33-35] After the development of RV-PA uncoupling, RV cannot pump blood efficiently against the afterload and progression of disease in these patients leads to the addition of heart failure symptoms.[32] Of note, RV-PA uncoupling is associated with increased mortality in patients with advanced pulmonary disease and PAH.[16,36]

Recent studies have shown that the RV-PA junction has a significant reserve and RV volume is maintained until the Ees/Ea ratio decreases from 1.5-2 to 0.8.[11] Therefore, the Ees/Ea ratio may help to predict right heart failure in PH.[8,9] However, measuring the Ees/Ea ratio through pressure-volume loops is invasive, technically difficult and costly. Therefore, the TAPSE/PASP ratio has been considered as the equivalent of Ees/Ea, considering that TAPSE measured by non-invasive echocardiography predicts contractility and PASP predicts afterload.[12-14] Previous studies have also demonstrated that the TAPSE/PASP ratio is a valuable parameter in predicting disease prognosis in patients with heart failure and PAH in whom right heart overload is critical in the disease

course.[10,12-14] According to the latest ESC/European Respiratory Society (ERS) PH guidelines, the TAPSE/PASP ratio is considered a prognostic factor in predicting prognosis in PH patients.[24] In addition, TAPSE/PASP ratio has been shown to be predictive of mortality in patients with acute heart failure, amyloidosis, patients undergoing LV assist device (LVAD) implantation, and patients undergoing transcatheter aortic valve implantation.[15-21] According to our study, the TAPSE/PASP ratio also predicts mortality in patients listed for LTx.

Tello et al.[36] found the cut-off value for RV-PA mismatch (Ees/Ea <0.805) to be 0.31 mm/mmHg in severe PAH patients and associated TAPSE/PASP <0.31 mm/mmHg with increased mortality in severe PAH. Ishii et al.[16] found the optimal cut-off value for TAPSE/PASP to be 0.30 mm/mmHg in a study performed in PAH patients who were LTx candidates and found mortality to be significantly higher in the group with TAPSE/PASP <0.30 mm/mmHg. In our study, we found the optimal cut-off value of the TAPSE/PASP ratio for mortality to be 0.29 mm/mmHg and showed that a decrease in the TAPSE/PASP ratio was associated with an increased mortality. Our cut-off value is similar to the cut-off values determined for PH patients in previous studies.[11,16]

According to the 2022 ESC/ERS PAH diagnosis and treatment guidelines, patients with a TAPSE/PASP ratio <0.19 mm/mmHg are classified as high-risk, with a reported one-year mortality rate exceeding 20%.[24] However, in our study, we found that, when the TAPSE/PASP ratio was <0.29 mm/mmHg, the one-year mortality rate was 47.8%. This discrepancy may be related to sample selection. Given the differences in mortality observed in patients undergoing LTx for PAH, we suggest that the TAPSE/PASP ratio should be reconsidered while selecting candidates for LTx, and further cohort studies are needed to explore this issue.

There are some limitations to this study. Although the hospital where the study was conducted is the largest LTx center in Türkiye, the single-center, retrospective design of our study is one of the major limitations. In addition, dynamic changes in the TAPSE/PASP ratio during follow-up may be valuable in predicting prognosis; however, due to the design of our study, we were unable to evaluate changes in the TAPSE/PASP ratio. Further multi-center, large-scale, long-term, prospective studies may be needed to confirm these findings.

In conclusion, the TAPSE/PASP ratio as a marker right ventricle-pulmonary artery uncoupling seems to be an independent predictor of long-term mortality in patients listed for lung transplantation. A TAPSE/PASP value below the cut-off value (0.29 mm/mmHg) is associated with a higher risk status and increased mortality during follow-up in this patient population.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplementary Table 1. Distribution of echocardiography and cardiac catheterization data according to TAPSE/PASP categories by linear model ANOVA test

	TAPSE/PASP ratio >0.55 mm/mmHg (n=64)	TAPSE/PASP ratio <0.55 mm/mmHg (n=109)	Overall population (n=173)	
Variables	Mean±SD	Mean±SD	Mean±SD	*p*
PASP on echocardiography (mmHg)	34.6±13.2	57.4±29.6	48.9±27.1	<0.001
LVEF (%)	63.8±4.0	63.5±4.1	63.6±4.0	0.59
PASP on cardiac catheterization (mmHg)	29.8±6.1	55.4±24.8	45.9±23.6	<0.001
mPAP on cardiac catheterization (mmHg)	17.9±4.7	33±15.1	27.4±14.3	<0.001
dPAP on cardiac catheterization (mmHg)	10.2±3.7	19.7±11.0	16.2±10.1	<0.001
Cardiac output (lt/dk)	4.5±0.9	4.4±1.1	4.4±1.0	0.74
Cardiac index (lt/dk/m^2)	2.6±0.5	2.6± 0.6	2.6±0.6	0.84
Right atrial mean pressure (mmHg)	4.7±2.1	6.1±4.0	5.6±3.5	0.01
Heart rate (beats per min)	88.5±17.8	87±13.7	87.6±15.3	0.52
LVEDP (mmHg)	9.1±4.4	10.9±4.2	10.2±4.4	0.01
PVR (WU)	2.5±1.8	4.6±3.0	3.8±2.8	<0.001
SVR (WU)	23.3±7.2	21.8±6.7	22.4±6.9	0.18
TAPSE (mm)	2.1±0.3	1.7±0.3	1.9±0.4	<0.001

TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary artery systolic pressure; ANOVA: Analysis of variance; SD: Standard deviation; LVEF: Left ventricular ejection fraction; mPAP: Mean pulmonary artery pressure; dPAP: Diastolic pulmonary artery pressure; LVEDP: Left ventricular end-diastolic pressure; PVR: Pulmonary vascular resistance; WU: Wood units; SVR: Systemic vascular resistance.

Supplementary Table 2. Distribution of spirometry and 6MWD data according to TAPSE/PASP categories by linear model ANOVA test

Variables	TAPSE/PASP ratio >0.55 mm/mmHg (n=64) Mean±SD	TAPSE/PASP ratio <0.55 mm/mmHg (n=109) Mean±SD	Number of total patients (n=173) Mean±SD	*p*
FEV1 (%)	43±11	45±14	44±13	0.31
FVC (%)	44±11	46±13	45±12	0.88
FEV1/FVC (%)	81±21	84±24	82±22	0.81
6MWD walk distance (meters)	313.5±104.5	297.8±92.7	303.6±97.2	0.30
6MWD baseline heart rate (beats/min)	87.4±8.9	86.7±9.5	87.0±9.3	0.61
6MWD end-of-test heart rate (beats/min)	104.7±14.3	103.2±14.2	103.8±14.2	0.51
6MWD baseline saturation (%)	94.4±2.5	93.5±4.7	93.8±4.0	0.18
6MWD end-of-test saturation (%)	82.9±6.3	81.8±7.6	82.2±7.1	0.34

TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary artery systolic pressure; ANOVA: Analysis of variance; SD: Standard deviation; FEV1: Forced expiratory volume in 1st second; FVC: Forced vital capacity; 6MWD: Six-minute walk distance.

Supplementary Table 3. Survival rates at 1, 3 and 5 years in patients with TAPSE/PASP >0.29 mm/mmHg and TAPSE/PASP <0.29 mm/mmHg

Group	Time (month)	Survival rate (%)	95% CI
TAPSE/PASP >0.29 mm/mmHg	12	80.1	73.6-87.1
TAPSE/PASP >0.29 mm/mmHg	36	56.5	48.5-65.7
TAPSE/PASP >0.29 mm/mmHg	60	46.7	38.1-57.2
TAPSE/PASP <0.29 mm/mmHg	12	52.2	37.3-73
TAPSE/PASP <0.29 mm/mmHg	36	26.6	14.4-49.2
TAPSE/PASP <0.29 mm/mmHg	60	14.3	5.5-37.1

TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary artery systolic pressure; CI: Confidence interval.