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The Usefulness of the TAPSE/sPAP Ratio for Predicting Survival in Medically Treated Chronic Thromboembolic Pulmonary Hypertension

Medikal Olarak Tedavi Edilen Kronik Tromboembolik Pulmoner Hipertansiyonda Sağkalımı Öngörmede TAPSE/sPAP Oranının Yararı

ABSTRACT

Objective: The ventriculoarterial uncoupling has been linked with unfavorable results as measured noninvasively by tricuspid annular plane systolic excursion divided by systolic pulmonary artery pressure (TAPSE/sPAP). However, its prognostic importance in chronic thromboembolic pulmonary hypertension (CTEPH) is limited. Thus, we determine the effect of the TAPSE/sPAP ratio on outcomes and predictors of all-cause mortality in these patients.

Methods: We analyzed 56 subjects with medically treated CTEPH. Two-dimensional echocardiographic examination and right heart catheterization findings were recorded from the hospital database. Baseline New York Heart Association functional class (NYHA-FC), 6-min walk distance (6MWD), and brain natriuretic peptide (BNP) test results were recorded.

Results: The median age was 65.5 years. Over a median follow-up time of 27 months, 29 (51.8%) patients died. BNP values were higher (P = 0.008), 6MWD values were lower (P = 0.004), and NHYA-FC (P = 0.0001) was worse in the non-survivor group. TAPSE (P = 0.0001) and TAPSE/sPAP ratio (P = 0.001) were significantly lower and pulmonary vascular resistance (PVR) was higher in the non-survivor group (P = 0.03). The best cut-off value for the TAPSE/sPAP ratio for predicting mortality was 0.20 mm/mmHg and the survival rates were significantly lower in the TAPSE/sPAP ratio ≤0.20 group (log-rank P = 0.012). 6MWD (P = 0.005), NHYA-FC III-IV (P = 0.0001), TAPSE/sPAP ratio ≤0.20 (P = 0.017), PVR (P = 0.008), and TAPSE/sPAP ratio ≤0.20 combined with NYHA-FC III-IV (P = 0.0001) were significant determinants and TAPSE/sPAP ratio ≤0.20 combined with NYHA-FC III-IV was the only independent predictor of mortality (P = 0.003).

Conclusion: Medically treated CTEPH patients with a TAPSE/sPAP ratio ≤0.20 had lower survival rates. TAPSE/sPAP ratio≤0.20 combined with NYHA-FC III-IV was the independent predictor of poor prognosis.

Keywords: Chronic thromboembolic pulmonary hypertension, mortality, tricuspid annular plane systolic excursion divided by systolic pulmonary artery pressure ratio

ÖZET

Amaç: Ventriküloarteriyel ayrılmayı gösteren, noninvaziv olarak ölçülen triküspid anüler düzlem sistolik hareketinin sistolik pulmoner arter basıncına bölünmesi ile elde edilen TAPSE/sPAP oranının olumsuz sonuçlarla ilişkili olduğu gösterilmiştir. Ancak TAPSE/sPAP oranının kronik tromboembolik pulmoner hipertansiyon (KTEPH) hastalarındaki prognostik değeri sınırlıdır. Bu çalışmada KTEPH hastalarında TAPSE/sPAP oranının prognoz üzerine etkisi ve bu hastalarda mortalite prediktörlerinin belirlenmesi amaçlanmıştır.

Yöntem: Medikal olarak tedavi edilen 56 KTEPH olgusu analiz edildi. İki boyutlu ekokardiyografik inceleme ve sağ kalp kateterizasyon bulguları hastane veritabanından kaydedildi. New York Kalp Derneği fonksiyonel sınıfı (NYHA-FS), 6 dakika yürüme mesafesi (6DYM) ve beyin natriüretik peptid (BNP) testi sonuçları kaydedildi.

Bulgular: Olguların medyan yaşı 65,5 yıldı. Medyan 27 aylık takip süresi boyunca 29 (%51.8) hastada mortalite gözlendi. Hayatta olmayan grupta BNP değerleri anlamlı olarak daha yüksek (P = 0.008), 6DYM değerleri daha düşüktü (P = 0.004) ve NHYA-FS değerleri daha kötüydü (P = 0.0001). TAPSE (P = 0.0001) ve TAPSE/sPAP oranı (P = 0.001) hayatta olmayan grupta anlamlı olarak daha düşük ve pulmoner vasküler direnç (PVR) anlamlı olarak daha yüksekti (P = 0.03). Mortaliteyi öngörmek için TAPSE/sPAP oranı için en iyi kesme değeri 0.20 mm/mmHg idi ve sağkalım oranları TAPSE/sPAP oranı ≤0.20 grubunda anlamlı olarak daha düşüktü (log-rank P = 0.012). Mortalite belirleyicileri 6DYM (P = 0.005), NHYA-FS III-IV (P = 0.0001), TAPSE/

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sPAP oranı ≤0.20 (*P* = 0.017), PVR (*P* = 0.008) ve NYHA-FS III-IV ile birlikte TAPSE/sPAP oranı ≤0.20 (*P* = 0.0001) idi ve NYHA-FS III-IV ile birlikte TAPSE/sPAP oranı ≤0.20'nin tüm nedenlere bağlı mortalitenin bağımsız anlamlı belirleyicisi olduğu gösterildi (*P* = 0.003).

Sonuç: TAPSE/sPAP oranı ≤0.20 mm/mmHg olan medikal olarak tedavi edilen KTEPH hastalarında sağkalım oranları anlamlı olarak daha düşük saptanmıştır. NYHA-FS III-IV ile birlikte TAPSE/sPAP oranı ≤0.20'nin altıda olmasının kötü prognozun tek bağımsız öngörücüsü olduğu gösterilmiştir.

Anahtar Kelimeler: Kronik tromboembolik pulmoner hipertansiyon, mortalite, TAPSE/sPAP oranı

Chronic thromboembolic pulmonary hypertension (CTEPH) is a subgroup of pre-capillary pulmonary hypertension (PH) in which flow-limiting organized thrombi chronically occlude pulmonary arteries (PA) and finally preceding raised pulmonary vascular resistance (PVR).[1] Pulmonary endarterectomy (PEA) is the cornerstone in the management of these subjects and specific PH treatment and balloon pulmonary angioplasty (BPA) are reserved for subjects who were considered inoperable or have ongoing or recurrent PH after surgery.[2]

Irrespective of the etiology, PH causes right ventricular (RV) pressure overload and impairment. The reduced RV function was determined as the cardinal component of prognosis in CTEPH patients.[3] Echocardiography is an essential imaging technique for all PH patients for identifying RV failure and dysfunction.

Several echocardiographic parameters including right atrial area, tricuspid regurgitation (TR), and presence of pericardial effusion have prognostic significance in Group 1 PH patients.[4] Tricuspid annular systolic plane excursion to systolic PA pressure (TAPSE/sPAP) ratio, which indicates RV-PA coupling, has recently been introduced in current PH guidelines as a prognostic echocardiographic parameter in Group 1 PH patients.[4] The decreased TAPSE[5] and TAPSE/sPAP ratio was identified to be linked with unfavorable outcomes in patients with CTEPH;[6] however, the evidence about the prognostic significance of these echocardiographic variables in medically treated CTEPH patients was limited in the literature.

Therefore, we proposed to determine the prognostic utility of the TAPSE/sPAP ratio and determinants of all-cause mortality only in medically treated CTEPH patients.

ABBREVIATIONS

6MWD	6-min walk distance
AUC	Area under the curve
BNP	Brain natriuretic peptide
BPA	Balloon pulmonary angioplasty
CI	Cardiac index
CI	Confidence intervals
CO	Cardiac output
CTEPH	Chronic thromboembolic pulmonary hypertension
dPAP	Diastolic pulmonary artery pressure
Ea	Arterial elastance
Ees	End-systolic elastance
ESC/ERS	European Society of Cardiology/European Respiratory Society
HF	Heart failure
HR	Hazard ratios
IVC	Inferior vena cava
mPAP	Mean PA pressure
NYHA-FC	New York Heart Association functional class
PA	Pulmonary arteries
PCWP	Pulmonary capillary wedge pressure
PEA	Pulmonary endarterectomy
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RAA	Right atrial area
ROC	Receiver-operating characteristic
RV	Right ventricular
sPAP	Systolic pulmonary artery pressure
TAPSE/sPAP	Tricuspid annular systolic plane excursion to systolic pulmonary artery pressure
TR	Tricuspid regurgitation
TRV	Tricuspid regurgitation velocity

Materials and Methods

Patients

We retrospectively reviewed 80 patients with CTEPH who were followed at our institutional PH clinic between January 2012 and February 2023. Patients who underwent PEA, BPA, and had missing echocardiographic data were excluded from the study. Patients with heart failure (HF) with reduced ejection fraction, active malignancy, and significant mitral and aortic valve diseases were also excluded from the study. The remaining medically treated 56 subjects with inoperable CTEPH or patients who refused surgery were included in this analysis. CTEPH was diagnosed in patients with invasively measured mean PA pressure (mPAP) ≥25 mmHg and pulmonary capillary wedge pressure (PCWP) <15 mmHg and perfusion defects determined by computed tomography pulmonary angiography, conventional pulmonary angiography, and ventilation-perfusion scintigraphy after minimum 3 months of efficacious anticoagulation treatment. All patients were incident patients that were diagnosed in our PH clinic and baseline characteristics, laboratory data, echocardiographic, and hemodynamic data were obtained from their first diagnostic work-up studies before PH-specific treatment.

The baseline data included demographics, anthropometric measurements, brain natriuretic peptide (BNP) values, 6-min walk distance (6MWD), New York Heart Association functional class (NYHA-FC), and medications. The patients were also divided into low, intermediate, and high risk, consistent with the European Society of Cardiology/European Respiratory Society (ESC/ERS) three-strata risk stratification tool. Since death certificates were not available for all patients who died, all-cause mortality was preferred as the outcome to avoid misinterpretation of the cause of death. Death from any cause was defined as all-cause mortality. The institutional electronic medical recording system and national mortality information system were used to determine the survival status and the date of death. The follow-up interval was decided as the time between the date of diagnosis and death or the last clinical visit.

Our institutional ethics committee approved this analysis and followed the rights specified in the Declaration of Helsinki.

Echocardiographic Examination and Invasive Measurements

The two-dimensional echocardiographic examination was conducted with a Philips Affinity 50 ultrasound system (Philips, Andover, MA, USA) using a 3.2 MHz transducer. A comprehensive echocardiography was performed for the right heart according to

the appropriate guidelines.[7] In the apical four-chamber view, an M-mode cursor was set along the lateral part of the tricuspid annulus, and the maximum movement during systole was determined as TAPSE. Continuous wave Doppler was used for recording the TR velocity (TRV) and the maximum TR gradient was calculated by the modified Bernoulli equation [4 × TRV^2]. The inferior vena cava (IVC) was viewed from the subcostal view and RA pressure was estimated using the inspiratory magnitude of IVC collapse and the size of the IVC.[8] The RA pressure was added to the expected peak TR gradient and recorded as sPAP. Then, TAPSE/sPAP ratio was computed for all subjects. European Association of Cardiovascular Imaging suggestions for native valvular regurgitation evaluation was used for grading TR severity.[9] The existence of pericardial effusion was also recorded. Invasive hemodynamics was carried out by a skilled cardiologist while the patient was at rest. The following measurements were acquired: RA pressure, PCWP, mean, diastolic, and systolic PA pressures (mPAP, dPAP, and sPAP, respectively). Blood gas analyses were obtained. The cardiac output (CO) was assessed using the indirect Fick method. PVR was measured as mPAP-PCWP divided by CO and the cardiac index (CI) as CO divided by body surface area. Echocardiographic and hemodynamic data were recorded from the electronic hospital database.

Data Analysis

The data analysis was performed with SPSS version 26 (SPSS Inc., Chicago, IL). Histograms and the Kolmogorov–Smirnov test validated the normal distribution of continuous variables. The continuous data were shown as median (interquartile range) and means ± standard deviations. Three tests were utilized to assess differences between groups: the Chi-square test, Mann–Whitney U test, and the Student's t-test where suitable. Variables from these analyses with $P < 0.1$ were utilized for univariate Cox proportional-hazard models. We estimated 95% confidence intervals (CI) for hazard ratios (HR) using univariate and multivariate Cox proportional-hazard models. The clinically related variables that were found significant in the univariate analysis were added to the multivariate analysis. Before multivariate analysis, we checked multicollinearity and avoided adding independent variables that highly correlate or contain each other. Using receiver-operating characteristic (ROC) curves, the effectiveness of the TAPSE/sPAP ratio in predicting mortality was evaluated. The values of the area under the curve (AUC) were estimated. $P < 0.05$ was used for deciding the statistical significance.

Results

We retrospectively enrolled 56 consecutive subjects with medically treated CTEPH. The overall median follow-up period was 27 months, and 51.8% (n = 29) of all-cause mortality was noted. The median age of the whole group was 65.5 years (58–75, interquartile range), and 60.7% (n = 34) of the patients were women. Most of the patients (n = 30) received riociguat therapy. Among baseline characteristics, BNP values were higher (420 [140–781] vs. 134 [47–420], $P = 0.008$), and 6MWD values were lower (165 [80–300] vs. 345 [232–450], $P = 0.004$) in the deceased group (Table 1). The deceased group also had a worse NHYA-FC ($P = 0.0001$), and the median follow-up time was lower as expected in this group (8 [3.5–26] vs. 58 [39–76], $P = 0.0001$).

Table 1. Baseline Characteristics of all Patients and Comparison between Survivor and Non-survivor Groups

	All patients (n = 56)	Survivors (n = 27)	Non-survivors (n = 29)	*P*
Age† (years)	65.5 (58–75)	63 (58–77)	67 (57–74)	0.53
Women, n (%)	34 (60.7)	15 (55.6)	19 (65.5)	0.44
BMI* (kg, m^2)	28.7 ± 6.8	29.4 ± 6.1	28.1 ± 7.6	0.5
Hypertension, n (%)	27 (48.2)	13 (48.1)	14 (48.3)	0.9
Diabetes mellitus, n (%)	13 (23.2)	6 (22.2)	7 (24.1)	0.8
COPD, n (%)	18 (32.1)	10 (37)	8 (27.6)	0.4
CAD, n (%)	10 (17.9)	6 (22.2)	4 (13.8)	0.4
BNP† (pg/mL)	282 (83–659)	134 (47–420)	420 (140–781)	**0.008**
6MWD† (m)	240 (100–400)	345 (232–450)	165 (80–300)	**0.004**
NHYA Functional class, n (%)				**0.0001**
Class I–II	25 (44.6)	21 (77.8)	4 (13.8)	
Class III - IV	31 (55.4)	6 (22.2)	25 (86.2)	
Medications, n (%)				
Bosentan	13 (23.2)	6 (22.2)	7 (24.1)	0.8
Ambrisentan	3 (5.4)	1 (3.7)	2 (6.9)	NA
Iloprost	3 (5.4)	1 (3.7)	2 (6.9)	NA
Epoprostenol	1 (1.8)	0 (0)	1 (3.4)	NA
Sildenafil	3 (5.4)	0 (0)	3 (10.3)	NA
Riociguat	30 (53.6)	18 (66.7)	12 (41.4)	0.07
CCB	4 (7.1)	1 (3.7)	3 (10.3)	NA
Follow-up time† (months)	27 (6–60)	58 (39–76)	8 (3.5–26)	**0.0001**

*, Mean ± standard deviation, †, Median (interquartile range). 6MWD, 6-min walk distance; BMI, Body mass index; BNP, Brain natriuretic peptide; CCB, calcium channel blocker; CAD, Coronary artery disease; COPD, Chronic obstructive pulmonary disease; NA, Non-applicable; NHYA, New York Heart Association.

The comparison of echocardiographic and hemodynamic data in survivor and non-survivor groups is represented in Table 2. Among echocardiographic variables, TAPSE (20.3 ± 4.7 vs. 15.3 ± 4.2, *P* = 0.0001), and TAPSE/sPAP ratio (0.29 ± 0.12 vs. 0.19 ± 0.08, *P* = 0.001) were significantly higher in the survivor group. However, there was no significant difference in sPAP values (77.5 ± 22 vs. 86.3 ± 19.4, *P* = 0.12) between the two groups. Among hemodynamic variables, only PVR was significantly higher in the non-survivor group (9.8 [6.7–14.2] vs. 7.8 [4.2–10], *P* = 0.03).

ROC analysis demonstrated that the AUC for the TAPSE/sPAP ratio for predicting mortality was 0.74 (95% CI 0.616–0.872, *P* = 0.002), and the optimal cut-off value of 0.20 mm/mmHg, specificity, and sensitivity 70% and 62%, respectively (Figure 1). Furthermore, survival was considerably lower in subjects with TAPSE/sPAP ratio levels equal to or <0.20 mm/mmHg (log-rank *P* = 0.012) (Figure 2). Survival rates for patients with lower TAPSE/sPAP ratio were 50% at 1 year, 46% at 2 years, 32% at 5 years, and 21% at 8 years. However, patients with TAPSE/sPAP ratio >0.20 mm/mmHg had survival rates of 90% at 1 year, 74% at 2 years, 60% at 5 years, and 52% at 8 years, respectively.

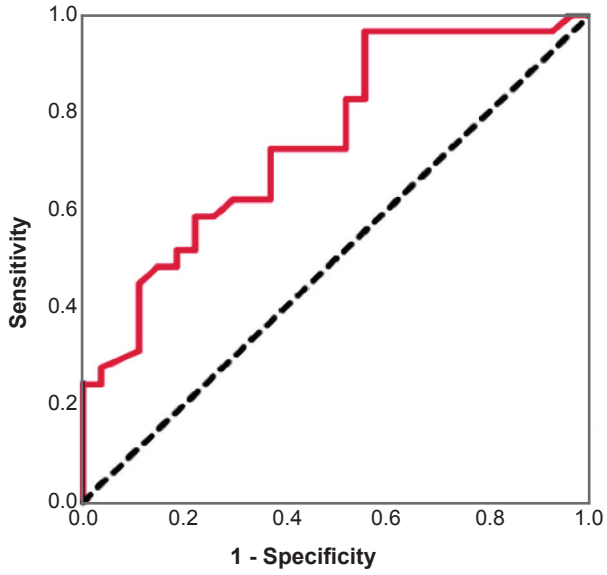

Figure 1. Receiver-operator-curve analysis of tricuspid annular plane systolic excursion divided by systolic pulmonary artery pressure ratio for the prediction of mortality.

Table 2. The Comparison of Echocardiographic and Hemodynamic Parameters in Survivor and Non-survivor Groups

	Survivors (n = 27)	Non-survivors (n = 29)	*P*
Echocardiographic data			
RV diameter* (mm)	38.5 ± 8.2	37.6 ± 7.8	0.68
RV FAC* (%)	27.7 ± 10.9	24.9 ± 11.5	0.46
TAPSE* (mm)	20.3 ± 4.7	15.3 ± 4.2	**0.0001**
RV S'* (cm/s)	10.6 ± 2.5	11.6 ± 4	0.32
Right atrial area* (cm^2)	25 ± 9.3	29.5 ± 8.7	0.13
sPAP* (mmHg)	77.5 ± 22	86.3 ± 19.4	0.12
TAPSE/sPAP* (mm/mmHg)	0.29 ± 0.13	0.19 ± 0.08	**0.001**
Tricuspid regurgitation n, %			0.08
Mild	12 (44.5)	7 (24.1)	
Moderate	5 (18.5)	13 (44.8)	
Severe	10 (37)	9 (31)	
Pericardial effusion n, %	3 (11.1)	7 (24.1)	0.2
LVEF† (%)	60 (60–65)	60 (60–65)	0.17
Hemodynamic data			
sPAP * (mmHg)	75.9 ± 22.1	81.8 ± 18.1	0.29
mPAP* (mmHg)	40.6 ± 12.5	45.3 ± 12.9	0.18
dPAP* (mmHg)	26.5 ± 12.4	31.8 ± 10.5	0.1
PCWP† (mmHg)	11 (10–13)	10 (9–13)	0.54
PVR† (Woods)	7.8 (4.2–10)	9.8 (6.7–14.2)	**0.03**
CO* (L/min)	4 ± 1.1	3.8 ± 1.7	0.7
CI* ($L/min/m^2$)	2.6 ± 1.7	2.2 ± 0.8	0.36
Right atrial pressure* (mmHg)	10 ± 5.9	11.5 ± 6.1	0.36
MVO^2* (%)	61.2 ± 8.6	60.4 ± 11.9	0.8

*, Mean ± standard deviation; †, Median (interquartile range). RV, Right ventricle; S', Systolic velocity; FAC, Fractional area change; TAPSE, Tricuspid annular plane systolic excursion; sPAP, Systolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; PCWP, Pulmonary capillary wedge pressure; PVR, Pulmonary vascular resistance; CO, Cardiac output; CI, Cardiac index; MVO^2, Mixed venous oxygen saturation; LVEF, Left ventricular ejection fraction.

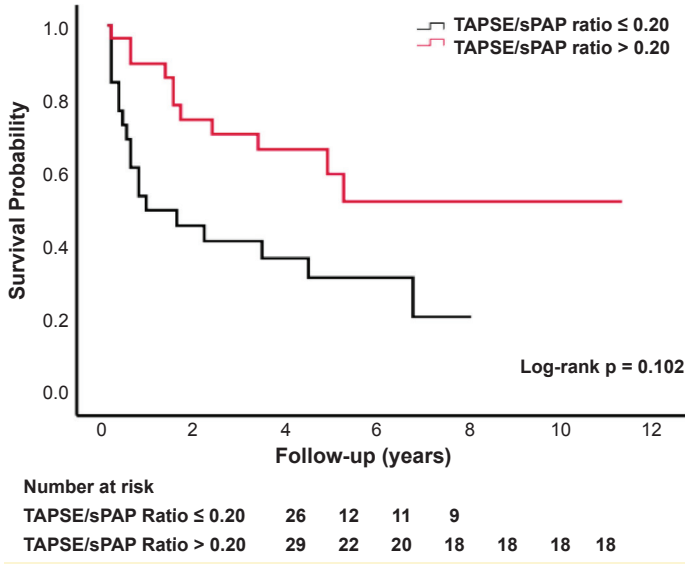

Figure 2. Kaplan–Meier survival curves for low and high tricuspid annular plane systolic excursion divided by systolic pulmonary artery pressure groups.

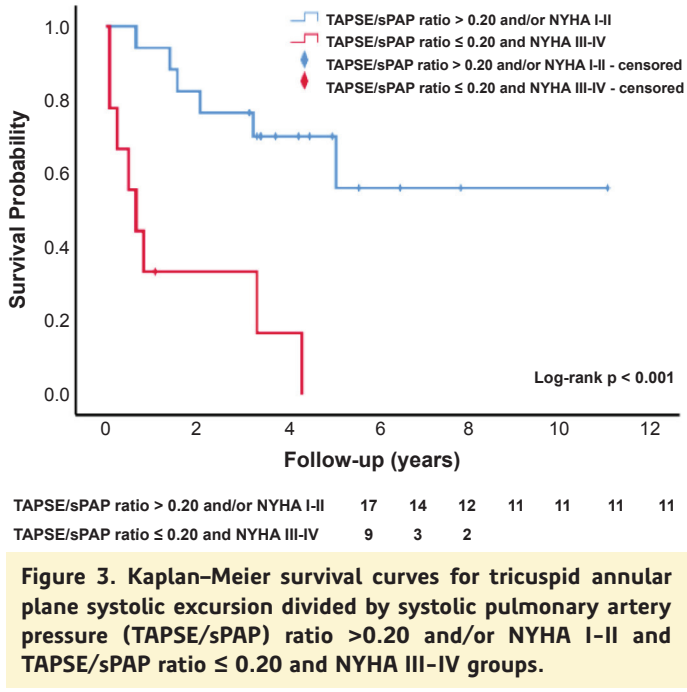

Figure 3. Kaplan–Meier survival curves for tricuspid annular plane systolic excursion divided by systolic pulmonary artery pressure (TAPSE/sPAP) ratio >0.20 and/or NYHA I-II and TAPSE/sPAP ratio ≤ 0.20 and NYHA III-IV groups.

Table 3. Univariate and Multivariate Determinants of All-cause Mortality in Patients with Medically Treated CTEPH

Variable	Univariate Cox regression analysis			Multivariate Cox Regression analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
BNP (pg/mL)	1.000	1.000–1.001	0.11	-	-	-
6MWD (m)	0.996	0.993–0.999	**0.005**	0.997	0.004–1.001	0.1
NYHA-FC III - IV	10.65	3.643–31.139	**0.0001**	-	-	-
TAPSE/sPAP ratio	0.001	0.000–0.118	**0.005**	-	-	-
TAPSE/sPAP ratio ≤0.20 mm/mmHg	2.5	1.177–5.312	**0.017**	-	-	-
Severe TR	1.527	0.566–4.121	0.4	-	-	-
dPAP (mmHg)	1.020	0.992–1.049	0.16	-	-	-
PVR (Woods)	1.115	1.029–1.209	**0.008**	1.093	0.999–1.197	0.053
TAPSE/sPAP ratio ≤0.20 mm/mmHg + NHYA-FC III-IV	6.305	2.955–13.455	**0.0001**	4.008	1.588–10.115	**0.003**

6MWD, 6-min walk distance; BNP, Brain natriuretic peptide; dPAP, diastolic pulmonary artery pressure; NHYA-FC, New York Heart Association Functional Capacity; PVR, Pulmonary vascular resistance; sPAP, Systolic pulmonary artery pressure; TAPSE, Tricuspid annular plane systolic excursion; TR, Tricuspid regurgitation.

Among all baseline, echocardiographic, and hemodynamic variables, NYHA-FC was found to be one of the most significant predictors of all-cause mortality. Survival was considerably lower in subjects with NHYA-FC III-IV (log-rank *P* = 0.0001). Survival rates for subjects with NYHA-FC I-II were 92% at 1 year, 88% at 2 years, 84% at 5 years, and 88% for 8 years. However, subjects with NYHA-FC III-IV had survival rates of 53% at 1 year, 37% at 2 years, and 14% at 5 years.

The univariate Cox regression analysis showed that 6MWD (HR 0.996 [0.993–0.999], *P* = 0.005), NHYA-FC III-IV (HR 10.65 [3.643–31.139], *P* = 0.0001), TAPSE/sPAP ratio (HR 0.001 [0.000–0.118], *P* = 0.005), TAPSE/sPAP ratio ≤0.20 (HR 2.5 [1.177–5.312], *P* = 0.017), PVR (HR 1.115 [1.029–1.209], *P* = 0.008), and TAPSE/sPAP ratio ≤0.20 combined with NYHA-FC III-IV (HR 6.305 [2.955–13.455], *P* = 0.0001) were significant determinants of all-cause mortality in medically treated CTEPH patients (Table 3). In addition, TAPSE/sPAP ratio ≤0.20 combined with NYHA-FC III-IV was found to be the only independent significant determinant of all-cause mortality in multivariate regression analysis (Table 3). Medically treated CTEPH patients with TAPSE/sPAP ratio ≤0.20 and NYHA-FC III-IV had a 4 times higher risk of death than those without TAPSE/sPAP ratio ≤0.20 and NYHA-FC III-IV.

According to the three-strata risk model outlined in 2022 ESC/ERS PH guidelines, 4 (6.8%) patients were in the low-risk category, 26 (44.8%) patients were in the intermediate-risk category, and 26 (44.8%) patients were in the high-risk category. Among the intermediate-risk group, survival was also

significantly lower in the TAPSE/sPAP ratio ≤0.20 and NYHA-FC III-IV group (log-rank *P* = 0.0001) (Figure 3). Survival rates for patients with TAPSE/sPAP ratio ≤0.20 and NYHA-FC III-IV were 33% at 1 year, 33% at 2 years, and 17% at 3 years. However, patients with TAPSE/sPAP ratio >0.20 and/or NYHA-FC I-II had survival rates of 94% at 1 year, 82% at 2 years, 70% at 5 years, and 56% at 8 years, respectively.

Discussion

This present work demonstrated that, among patients with medically treated CTEPH, the non-survivor group had a lower TAPSE/sPAP ratio than the survivor group and the best cut-off value of TAPSE/sPAP for predicting mortality in these patients was 0.20 mm/mmHg. The survival rates were considerably lower in patients in the low TAPSE/sPAP ratio group. The significant determinants of mortality in these subjects were NHYA-FC III-IV, 6MWD, TAPSE/sPAP ratio ≤0.20, PVR, and TAPSE/sPAP ratio ≤0.20 combined with NYHA-FC III-IV. In addition, TAPSE/sPAP ratio ≤0.20 combined with NYHA-FC III-IV was found to be the only independent significant determinant of mortality in medically treated CTEPH patients. Interestingly, among intermediate-risk patients according to the three-strata risk model, the subjects with TAPSE/sPAP ratio ≤0.20 and NYHA-FC III-IV had significantly higher mortality rates in contrast to the patients with TAPSE/sPAP ratio >0.20 and/or NYHA-FC I-II.

One of the cornerstone factors that significantly affect the outcomes in subjects with PH is reduced RV function.[4] The RV accommodates increased afterload by slight dilation with preserved stroke volume and systolic performance. At this phase, RV is coupled with pulmonary circulation. However, as PH progresses, the RV continues to enlarge, stroke volume and systolic performance decline, and the RV becomes uncoupled with pulmonary circulation.[10] The gold standard technique for the measurement of RV-PA coupling is end-systolic elastance (Ees), which is a marker of RV systolic performance, divided by arterial elastance (Ea), which is a marker of total load on RV.[10] The echocardiographic approximate of RV/PA coupling in PH patients can be achieved through the TAPSE/sPAP ratio.[11] TAPSE/sPAP ratio was also linked with long-term prognosis in Group 1 PH patients[12] and has been suggested as a new echocardiographic prognostic variable in current PH guidelines.[4] We have demonstrated that the TAPSE/sPAP ratio was reduced and the optimum cut-off value of TAPSE/sPAP for predicting mortality was 0.20 mm/mmHg in medically treated CTEPH patients. The mortality was significantly increased in the low TAPSE/sPAP group. In concordance with our results, Duan et al.[6] established that the TAPSE/sPAP ratio was an independent determinant of clinical worsening, specified as mortality, HF hospitalizations or deterioration of PH, and intensifying PH treatment, in 205 CTEPH patients. In this present work, the majority of the patients underwent PEA or BPA (61.4%), and only 7 (3.4%) patients died in a median follow-up of 1 year. The main superiority of our report was as follows, first, we included only medically treated CTEPH patients, as BPA[13] and PEA[14] significantly reduce mortality in CTEPH patients, and we examined more robust endpoints as all-cause mortality.

PVR, 6MWD, and NYHA-FC III-IV were shown to be relevant predictors of all-cause deaths in our cohort. Similar to our findings, 6MWD, NHYA-FC, and PVR were previously demonstrated as significant predictors of mortality in inoperable CTEPH patients.[15-17] However, among echocardiographic variables, only the TAPSE/sPAP ratio was linked with all-cause mortality in our cohort and the main difference arose from the TAPSE. TAPSE is an easily available echocardiographic parameter that reflects the longitudinal function of the RV. The predominant contraction of the RV is aligned with the longitudinal axis, rather than the short axis in the normal population.[18] This is not the case for patients with PH; however, Sato et al. [19] demonstrated that TAPSE was superior to other RV systolic function indices for determining RV ejection fraction evaluated with gold standard cardiac magnetic resonance imaging in PH patients. In addition, it has been shown that the deformation in the RV apical part was decreased in comparison with the basal part of the RV in PH patients.[20] The decreased deformation in the apical segment indicates that the systolic function of the apical segment of the RV free-wall decreases more profoundly than the basal segment in pressure-overloaded RV, which might explain the more significant decrease in TAPSE in our cohort.

We have demonstrated that NYHA-FC is one of the most important predictors of all-cause mortality; however, it has been shown that NYHA-FC has its limitations including, the inability to predict adverse cardiovascular events in HF patients and the subjectivity and poor reproducibility of this system.[21,22] Therefore, we proposed to combine NYHA-FC with TAPSE/sPAP ratio to assist physicians in better discriminating the patients with poor prognoses. One of the original findings of our report is that the TAPSE/sPAP ratio ≤0.20 combined with NYHA-FC III-IV independently predicts all-cause mortality in medically treated CTEPH patients. This result might be interpreted as combining NHYA-FC with the TAPSE/sPAP ratio might define a worse prognosis and the TAPSE/sPAP ratio might be more specific in determining RV dysfunction in medically treated CTEPH patients. More interestingly, our data demonstrated that combining NHYA functional class III-IV with a TAPSE/sPAP ratio ≤0.20 also indicates poor prognosis among intermediate-risk patients according to the three-strata risk model outlined in the 2022 ESC/ERS PH guidelines. It has already been shown that the main restriction of the three-strata risk model was that the majority of the PH patients were categorized into intermediate-risk, and high-intermediate-risk patients and had worse survival rates.[23] In intermediate-risk patients with medically treated CTEPH, combining NYHA FC with TAPSE/sPAP ratio identifies high-intermediate risk patients and this finding might assist physicians in guiding further management of these patients.

Strengths and Limitations

The main strengths of this study include the identification of an optimal cut-off value for the TAPSE/sPAP ratio in predicting mortality in medically treated CTEPH patients, the demonstration that TAPSE and the TAPSE/sPAP ratio might be more powerful than other echocardiographic parameters in indicating worse RV function in these patients, and the ability of TAPSE/sPAP ratio in the identification of high-intermediate-risk patients among intermediate-risk group according to the ESC/ERS risk stratification tool. In addition, this study might contribute to the pre-existing literature by demonstrating that the TAPSE/sPAP ratio, a new prognostic echocardiographic parameter in Group 1

PH patients, might also be used to identify patients with a worse prognosis in medically treated CTEPH patients.

The main limitations of our study were the retrospective design, which has its own inherent limitations, and the small number of patients. The study population is relatively small because we included patients who had adequate echocardiographic information and we solely enrolled medically treated CTEPH patients. Since this was a single-center study and CTEPH is a rare disease, we were able to identify 56 patients. Although the sample size is small for drawing robust conclusions, power analysis revealed a sufficient power of 92% in comparison to the TAPSE/sPAP ratio between survivors and non-survivors. We could not examine cardiovascular mortality to avoid misclassification of the deaths. Our study does not provide a true causal relationship due to the relatively small number of patients and the inability to adjust other possible confounding factors, including HF with preserved ejection fraction that might have affected the results. However, our results might serve as a pilot study that demonstrates the prognostic value of the TAPSE/sPAP ratio in medically treated CTEPH patients, as in Group 1 PH. We did not record the invasive Ees/Ea ratio for determining RV-PA coupling. TAPSE has been demonstrated to be weakly correlated with Ees;[24] however, the TAPSE/sPAP ratio has been shown to be an echocardiographic marker of RV-PA coupling in PH patients.[11] In addition, both TAPSE and sPAP measurements have their own limitations. TAPSE is load-dependent and might be overestimated in severe TR.[25] Severe TR might also lead to an underestimation of sPAP.[26] Nonetheless, we demonstrated the prognostic significance of the TAPSE/sPAP ratio in medically treated CTEPH patients, as in Group 1 PH.

Conclusion

This present work is one of the first preliminary reports that evaluated the prognostic significance of the TAPSE/sPAP ratio in medically treated CTEPH patients. Subjects with a TAPSE/sPAP ratio of ≤0.20 mm/mmHg had lower survival rates, and when added to NHYA-FC III-IV, this combination independently predicts all-cause mortality in these patients. This parameter might indicate rapid clinical deterioration in the follow-up of these patients and might point out the patients with a worse prognosis among intermediate-risk patients. Based on the evaluation of this readily available echocardiographic parameter, new and/or intensified treatment options, including BPA, may improve the prognosis of medically treated CTEPH patients. Future trials with larger cohorts were warranted for the validation of clinical usage of the TAPSE/sPAP ratio in prognostic determination in medically treated CTEHP patients.

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee of Dokuz Eylül University (Approval Number: 2023/15-14, Date: May 10, 2023).

Informed Consent: Written informed consent was obtained from the patients.

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References

1. Papamatheakis DG, Poch DS, Fernandes TM, Kerr KM, Kim NH, Fedullo PF. Chronic thromboembolic pulmonary hypertension: JACC focus seminar. *J Am Coll Cardiol.* 2020;76(18):2155-2169. [CrossRef]
2. Mullin CJ, Klinger JR. Chronic thromboembolic pulmonary hypertension. *Heart Fail Clin.* 2018;14(3):339-351. [CrossRef]
3. Marchetta S, Verbelen T, Claessen G, Quarck R, Delcroix M, Godinas L. A comprehensive assessment of right ventricular function in chronic thromboembolic pulmonary hypertension. *J Clin Med*. 2022;12(1):47. [CrossRef]
4. Humbert M, Kovacs G, Hoeper MM, et al.; ESC/ERS Scientific Document Group. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2022;43(38):3618-3731. Erratum in: *Eur Heart J.* 2023;44(15):1312. [CrossRef]
5. Küçükoğlu MS, Sinan ÜY, Yıldızeli B. Ten-year outcome of chronic thromboembolic pulmonary hypertension patients in a tertiary center. *Anatol J Cardiol.* 2020;23(2):105-109. [CrossRef]
6. Duan A, Li X, Jin Q, et al. Prognostic implication of noninvasive right ventricle-to-pulmonary artery coupling in chronic thromboembolic pulmonary hypertension. *Ther Adv Chronic Dis.* 2022;13:20406223221102803. [CrossRef]
7. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr.* 2010;23(7):685-713; quiz 786-788.
8. Beigel R, Cercek B, Luo H, Siegel RJ. Noninvasive evaluation of right atrial pressure. *J Am Soc Echocardiogr*. 2013;26(9):1033-1042. [CrossRef]
9. Lancellotti P, Tribouilloy C, Hagendorff A, et al.; Scientific Document Committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: An executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2013;14(7):611-644. [CrossRef]
10. Vonk Noordegraaf A, Chin KM, Haddad F, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: An update. *Eur Respir J.* 2019;53(1):1801900. [CrossRef]
11. Tello K, Wan J, Dalmer A, et al. Validation of the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio for the assessment of right ventricular-arterial coupling in severe pulmonary hypertension. *Circ Cardiovasc Imaging.* 2019;12(9):e009047. [CrossRef]
12. Kazimierczyk R, Kazimierczyk E, Knapp M, et al. echocardiographic assessment of right ventricular-arterial coupling in predicting prognosis of pulmonary arterial hypertension patients. *J Clin Med.* 2021;10(13):2995. [CrossRef]
13. Taniguchi Y, Jaïs X, Jevnikar M, et al. Predictors of survival in patients with not-operated chronic thromboembolic pulmonary hypertension. *J Heart Lung Transplant.* 2019;38(8):833-842. [CrossRef]
14. Delcroix M, Lang I, Pepke-Zaba J, et al. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *Circulation.* 2016;133(9):859-871. [CrossRef]
15. Saouti N, de Man F, Westerhof N, et al. Predictors of mortality in inoperable chronic thromboembolic pulmonary hypertension. *Respir Med*. 2009;103(7):1013-1019. [CrossRef]
16. Taniguchi Y, Jaïs X, Jevnikar M, et al. Predictors of survival in patients with not-operated chronic thromboembolic pulmonary hypertension. *J Heart Lung Transplant.* 2019;38(8):833-842. [CrossRef]

17. Nishimura R, Tanabe N, Sugiura T, et al. Improved survival in medically treated chronic thromboembolic pulmonary hypertension. *Circ J*. 2013;77(8):2110-2117. [CrossRef]
18. Rushmer RF, Crystal DK, Wagner C. The functional anatomy of ventricular contraction. *Circ Res*. 1953;1(2):162-170. [CrossRef]
19. Sato T, Tsujino I, Ohira H, et al. Validation study on the accuracy of echocardiographic measurements of right ventricular systolic function in pulmonary hypertension. *J Am Soc Echocardiogr.* 2012;25(3):280-286. [CrossRef]
20. Dambrauskaite V, Delcroix M, Claus P, et al. Regional right ventricular dysfunction in chronic pulmonary hypertension. *J Am Soc Echocardiogr.* 2007;20(10):1172-1180. [CrossRef]
21. Caraballo C, Desai NR, Mulder H, et al. Clinical implications of the New York Heart Association Classification. *J Am Heart Assoc.* 2019;8(23):e014240. [CrossRef]
22. Raphael C, Briscoe C, Davies J, et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. *Heart.* 2007;93(4):476-482. [CrossRef]
23. Kylhammar D, Hjalmarsson C, Hesselstrand R, et al. Predicting mortality during long-term follow-up in pulmonary arterial hypertension. *ERJ Open Res.* 2021;7(2):00837-2020. [CrossRef]
24. Guihaire J, Haddad F, Boulate D, et al. Non-invasive indices of right ventricular function are markers of ventricular-arterial coupling rather than ventricular contractility: Insights from a porcine model of chronic pressure overload. *Eur Heart J Cardiovasc Imaging.* 2013;14(12):1140-1149. [CrossRef]
25. Li Y, Guo D, Gong J, et al. Right ventricular function and ıts coupling with pulmonary circulation in precapillary pulmonary hypertension: A three-dimensional echocardiographic study. *Front Cardiovasc Med.* 2021;8:690606. [CrossRef]
26. Rako ZA, Kremer N, Yogeswaran A, Richter MJ, Tello K. Adaptive versus maladaptive right ventricular remodelling. *ESC Heart Fail*. 2023;10(2):762-775. [CrossRef]