Utility of TAPSE/sPAP Ratio in Acute Pulmonary Embolism as Valuable Prognostic Marker as PESI Score

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ABSTRACT

Introduction: The pulmonary embolism severity index (PESI) score is used to determine the risk of mortality and severity of complications in acute pulmonary embolism (APE). Tricuspid annular plane systolic excursion/systolic pulmonary arterial pressure (TAPSE/sPAP) ratio has been recently shown to predict poor 30-day clinical outcome in APE. We aimed to analyze the prognostic value of the TAPSE/sPAP ratio for prediction of 30-day adverse clinical outcomes in APE patients, similar to PESI score.

Patients and Methods: This study enrolled 203 retrospectively evaluated patients (female 108, mean age= 57.4 ± 15.5 years) with the diagnosis of APE between 2010 and 2020. All patients underwent transthoracic echocardiography before specific APE treatment. Primary endpoints were 30-day mortality, thrombolytic therapy requirement, mechanical ventilation requirement, mental status deterioration, and persistent hypotension (systolic blood pressure <90 mmHg). The study population was divided into two groups according to the TAPSE/sPAP ratio= 114 patients in group 1 with a low TAPSE/sPAP ratio (<0.494) and 89 patients in group 2 with a high TAPSE/sPAP ratio (>0.494).

Results: The incidence of in-hospital mortality (4.4 vs. 0%, p= 0.045], 30-day mortality [n= 8 (7.0%); 0 (0%), p= 0.009] and primary adverse outcomes (35.1 vs. 0%, p< 0.001) were higher in group 1. The TAPSE/sPAP ratio was negatively correlated with PESI (r= -0.716, p< 0.001). In multivariate logistic regression analyses revealed that the TAPSE/sPAP ratio [OR= 0.001, 95C% CI= 0.000-0.476, p= 0.028] was an independent predictor of 30-day mortality in APE.

Conclusion: The present study showed that the TAPSE/sPAP ratio may be used in clinical practice for the prediction of short-term adverse outcome risk estimation in APE patients, similar to PESI score.

Key Words: Acute pulmonary embolism; echocardiography; hypotension; death; single center

Akut Pulmoner Emboli Hastalarında TAPSE/sPAP Oranının PESI Skoru Kadar Değerli Prognostik Bir Belirteç Olarak Kullanımı

ÖZET

Giriş: Akut pulmoner emboli (APE) kliniğinde hastane içi ve ilk ay mortalite ve morbidite öngördürücü olarak "pulmonary embolism severity index (PESI)" skoru kullanılmaktadır. Triküspid annüler düzlem sistolik hareketi/sistolik pulmoner arter basıncı (TAPSE/sPAP) oranının, APE'de son çalışmalarda 30 günlük kötü klinik sonlanım ile ilişkili olabileceği gösterilmiştir. Bu çalışmada TAPSE/sPAP oranının APE hastalarında PESI skoruna benzer şekilde mortalite ve morbidite öngördürücüsü olarak kullanılabilirliğinin araştırılması amaçlanmıştır.

Hastalar ve Yöntem: Bu çalışmaya 2010-2020 yılları arasında, tek merkezli, retrospektif (203 hasta, ortalama yaş= 57.4 ± 15.5 yıl) ve yeni tanı APE hastası alınmıştır. Daha önceden APE teşhis ve tedavisi alan hastalar çalışma dışı bırakılmıştır. Transtorasik ekokardiyografik değerlendirmeleri spesifik APE tedavisi başlamadan önce yapılmıştır. Çalışmanın primer sonlanım noktası 30 günlük mortalite, trombolitik tedavi ihtiyacı, sebat eden hipotansiyon (sistolik arteryel kan basıncı <90 mmhg), mekanik ventilatör ihtiyacı ve bozulmuş mental durum olarak belirlenmiştir. Hastalar TAPSE/sPAP oranına göre düşük TAPSE/sPAP oranı (<0.494) olan grup 1 (114 hasta) ve yüksek TAPSE/sPAP oranı (>0.494) ile grup 2 (89 hasta) olmak üzere iki gruba ayrılmıştır.

Bulgular: Hastane içi mortalite (4.4'e karşı %0, p= 0.045), 30 günlük mortalite (7'ye karşı %0, p= 0.009) ve birincil yan sonuçlar (35.1'e karşı %0, p< 0.001) grup 1'de daha yüksekti. TAPSE/sPAP oranı, PESI ile negatif korelasyon gösterdi (r= -0.716, p< 0.001). Çok değişkenli lojistik regresyon analizlerinde, TAPSE/sPAP oranının [OR= 0.001, 95C% CI= 0.000-0.476, p= 0.028] APE'de 30 günlük mortalitenin bağımsız bir belirleyicisi olduğu ortaya çıktı.

Sonuç: Bu çalışmada APE hastalarında TAPSE/sPAP oranının PESI skoruna benzer şekilde erken dönemde olumsuz klinik sonlanımları öngörmede kısa ve hızlı bir parametre olarak kullanılabileceği gösterilmiştir.

Anahtar Kelimeler: Akut pulmoner emboli; ekokardiyografi; hipotansiyon; ölüm; tek merkez

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INTRODUCTION

Acute pulmonary embolism (APE) caused by venous thromboembolism is the most common cardiovascular disease in the world after acute coronary syndrome and stroke[1]. In APE, the increase in the right ventricular (RV) afterload and RV dysfunction secondary to obstruction in the pulmonary vascular bed is the main cause of in-hospital and 30-day mortality[2]. Cardiogenic shock or hemodynamic instability at first admission is associated with increased mortality in APE patients[3]. However, not all APE patients are hemodynamically unstable at hospital admission. Therefore, in addition to early diagnosis, it is important to evaluate the short-term mortality risk in APE patients. Calculation of the pulmonary embolism severity index (PESI) score[4] to evaluate the mortality risk of APE patients at admission is recommended in the latest pulmonary embolism diagnosis and treatment guideline by the European Society of Cardiology[5]. Transthoracic echocardiography (TTE) in APE has become an indispensable diagnostic method in both early diagnosis and risk assessment[6,7]. Some TTE findings and criteria have been associated with an increased risk of mortality in APE[8]. Despite all these studies, no single echocardiographic parameter has been found to be fully effective in assessing the risk of mortality in APE patients. Tricuspid annular plane systolic excursion (TAPSE) shows longitudinal systolic contraction of the RV[9]. TAPSE is used as a prognostic tool in the course of many cardiac diseases. systolic pulmonary arterial pressure (sPAP) constitutes the afterload of RV. TAPSE/sPAP ratio, a new echocardiographic index, has become a parameter that included RV function and RV afterload, and thus provides information about RV performance. An increase in the ratio, approaching 1, indicates a favorable RV condition, whereas a decrease to less than 0.5 is associated with a poor prognosis in various cardiac diseases[10,11]. Recently, Lyhne et al. have reported that the TAPSE/sPAP ratio may be a short-term predictor of mortality in APE patients[12]. The goal of this study was to compare the PESI score, which shows the short-term mortality risk, and the TAPSE/sPAP ratio in APE patients.

PATIENTS and METHODS

This retrospective study was conducted in accordance with the principles of the Helsinki Declaration and approved by the local institutional ethics committee. Written informed consent was obtained from each patient. Clinical outcomes were analyzed in 203 patients with APE who were admitted or referred to our tertiary hospital between January 2010 and August 2020. Patients with a contraindication to thrombolytic therapy, onset of symptoms of >14 days, systemic arterial systolic blood pressure of <90 or >200 mmHg, end-stage liver disorder, severe thrombocytopenia (platelet count <50.000/mm^3), age <18, cardiogenic shock, poor image quality, chronic thromboembolic pulmonary hypertension patients, recurrent pulmonary embolism, moderate to severe aortic and mitral valve diseases, a history of cardiac surgery, advanced-stage heart failure, and congenital heart disease history were excluded from the study. Patients were also excluded if they had undergone thrombus-reducing therapy (e.g., thrombolysis) or received extracorporeal membrane oxygenation (ECMO) before undergoing echocardiography.

The flow chart for patient selection is summarized in Figure 1. The PESI score of the patients in this study was calculated based on the vital signs, clinical characteristics, and background information recorded at the time of their admission to the emergency service, prior to receiving treatment.

The echocardiographic parameters of the patients include the procedures performed in the first 24 hours after the diagnosis of APE and before specific treatment was started. The primary endpoints of the study are in-hospital and 30-day mortality, persistent hypotension (systolic blood pressure <90 mmHg lasting more than 10 minutes), thrombolytic therapy requirement, as well as mental status disorder due to coma and hypoperfusion (coma, stupor, and need for mechanical ventilator). Following discharge, patients were scheduled for a one-month outpatient clinic follow-up. In cases where patients did not attend this initial one-month check-up, they were contacted by phone to inquire about their health status, and if applicable, to ascertain the date of death. The study population was divided into two groups according to the TAPSE/sPAP ratio= 114 patients in group 1 with a low TAPSE/sPAP ratio (<0.494) and 89 patients in group 2 with a high TAPSE/sPAP ratio (>0.494).

Echocardiography

Transthoracic echocardiography (TTE) was performed within two hours of admission to the hospital.

The sPAP was calculated from the tricuspid regurgitation (TR) jet velocity in accordance with the modified Bernoulli equation without any degree of pulmonary valve stenosis and the right atrial pressure was estimated as 10, 15, and 18 mmHg for mild, moderate, and severe right atrial enlargement, respectively[13,14]. Tricuspid annular plane systolic excursion (TAPSE) was acquired by placing an M-mode cursor through the lateral tricuspid annulus and measuring the amount of longitudinal motion of the annulus at peak systole in the standard apical four-chamber view. In all patients, the right ventricular end-diastolic diameters were measured using the apical four-chamber view, and left ventricular end-diastolic diameters (LVEDD) were measured with M-mode

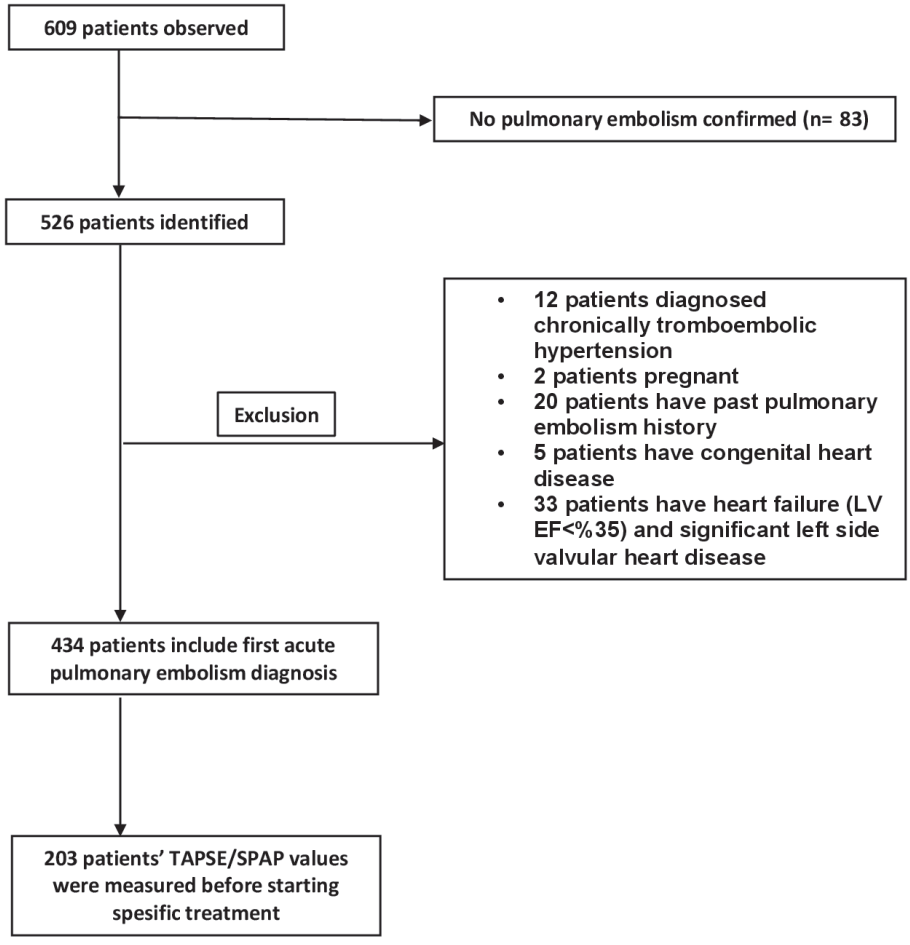

Figure 1. Flow chart of patient selection.

LVEF: Left ventricular ejection fraction, TAPSE: Tricuspid annular plane systolic excursion, sPAP: Systolic pulmonary arterial pressure.

echocardiography on the parasternal long-axis view. Left ventricle ejection fraction (LVEF) was calculated by using biplane Simpson's method[15]. The interpretation of the echocardiographic findings was carried out by a cardiologist who was blinded to the patients' treatment assignments. A dichotomous value of 40 mm Hg for sPAP was used to define pulmonary hypertension.

RV enlargement was defined as a right-to-left ventricular ratio (RV/LV) of ≥0.9[13,14].

Statistical Analysis

Statistical analysis was performed using the IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). The data were expressed as n (%) for categorical variables. The Pearson Chi-square and Fisher's exact tests were performed for categorical variables. After normal distribution was analyzed with the Kolmogorov-Smirnov test, the data were expressed as median (25^{th} and 75^{th} percentiles) for variables without a normal distribution and mean ± SD for variables with normal distribution. Student's t-test was used for comparing quantitative variables with normal distribution while the Mann-Whitney U test was used for comparing quantitative variables without normal distribution. Univariate and multivariate logistic regression analyses were used to determine the independent predictors of 30-day mortality and primary composite endpoints. Receiver operating characteristic (ROC) curve analysis was performed to identify the optimal TAPSE/sPAP ratio value that could predict mortality and primary composite outcomes with the highest sensitivity and specificity.

Simple linear regression analysis was used to determine the relation between the TAPSE/sPAP ratio and PESI score. Additionally, Spearman correlation analysis was used to predict the correlation between the TAPSE/sPAP ratio and other clinical variables. A p-value of <0.05 was considered statistically significant.

Table 1. Baseline clinical and demographical variables of the study population

Parameters	All patients (n= 203)	TAPSE/sPAP <0.494 (n= 114)	TAPSE/sPAP >0.494 (n= 89)	p value
Age	57.4 ± 15.5	60.77 ± 14.92	53.18 ± 15.39	**<0.001**
Gender (women), n (%)	108 (53.2)	68 (59.6)	40 (44.9)	**0.037**
Height (cm)	165 (160-174)	165 (160-170)	168 (160-175)	**0.028**
Weight (kg)	80 (72-90)	80 (70-90)	80 (75-90)	0.533
BMI (kg/m^2)	29.21 (26.12-32.59)	29.36 (26.30-33.20)	29.14 (26.12-31.60)	0.410
CRP	29.95 (11.9-63.75)	21.1 (11.0-42.8)	36.8 (13.6-75.0)	**0.025**
Hs-Troponin I (positive or negative)	90 (49.2)	69 (67.6)	21 (25.9)	**<0.001**
Hs-Troponin I Level	15 (6.9-90)	39 (10-106)	10 (1-23)	**<0.001**
Hb	13.1 (11.7-14.4)	13.1 (11.6-14.4)	13.2 (12.2-14.3)	0.930
Htc	39.43 ± 5.46	39.8 ± 5.8	39.0 ± 5.0	0.295
WBC	9.76 (8.02-11.83)	9.9 (8.1-11.8)	9.6 (8.0-11.7)	0.523
PLT	233 (199-290)	232 (185-282)	239 (210-304)	0.113
RDW	13.4 (12.5-14.7)	13.9 (13.0-15.7)	12.9 (12.4-13.8)	**<0.001**
Neut	6.5 (5.1-8.49)	6.93 (5.25-8.66)	6.34 (4.95-8.09)	0.195
Lym	2.03 (1.47-2.71)	2.00 (1.45-2.67)	2.13 (1.60-2.75)	0.275
NLR	3.22 (2.25-4.98)	3.5 (2.3-5.2)	3.0 (2.1-4.4)	0.141
ALT	21 (14-36)	22 (15-45)	17 (13-30)	**0.024**
AST	23 (16-35)	24 (17-39)	22 (15-32)	0.051
Creatinine	0.89 (0.72-1.10)	0.9 (0.8-1.1)	0.8 (0.7-1.0)	**0.024**
Urea	15 (12-21)	17 (13-24)	14 (11-19)	**0.005**
INR	1.1 (1.03-1.19)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	0.450
Systolic BP	124 (110-140)	120 (95-135)	130 (120-140)	**<0.001**
Diastolic BP	75 (67-83)	70.5 (60-80)	80 (70-87)	**0.004**
Hypotension	17 (8.4)	17 (14.9)	0 (0)	**<0.001**
Heart rate	96 (80-110)	103 (87-114)	89 (78-100)	**<0.001**
Pulse O_2 saturation	94 (88-96)	89 (87-94)	96 (94-97)	**<0.001**
Respiratory rate	22 (20-24)	23 (21-26)	21 (20-23)	**<0.001**
Body fever	36.3 (36.1-36.6)	36.3 (36.1-36.5)	36.4 (36.1-36.6)	**0.021**
Altered mental status	7 (3.4)	7 (6.1)	0 (0)	**0.016**
DVT	82 (40.4)	49 (43.0)	33 (37.1)	0.395
Smoking status	38 (18.7)	20 (17.5)	18 (20.2)	0.627
DM	47 (23.2)	34 (29.8)	13 (14.6)	**0.011**
HTN	92 (45.3)	54 (47.4)	38 (42.7)	0.507
CRF	18 (8.9)	10 (8.8)	8 (9.0)	0.957
CAD	32 (15.8)	18 (15.8)	14 (15.7)	0.991
CHF	20 (9.9)	18 (15.8)	2 (2.2)	**0.001**
COAD	23 (11.3)	16 (14.0)	7 (7.9)	0.169
History of cancer	10 (4.9)	6 (5.3)	4 (4.5)	0.535
Immobilization	25 (12.3)	13 (11.4)	12 (13.5)	0.655
Recent surgery history	14 (6.9)	6 (5.3)	8 (9.0)	0.299
Thrombolytic therapy	30 (14.8)	30 (26.3)	0 (0)	**<0.001**
Anticoagulant therapy category	163 (80.3)	84 (73.7)	79 (88.8)	**0.007**
Subgroup				
Warfarin	176 (86.7)	102 (89.5)	74 (83.1)	
NOAC	17 (8.4)	7 (6.1)	10 (11.2)	0.465
LMWH	10 (4.9)	5 (4.4)	5 (5.6)	

BMI: Body mass index, CRP: C-reactive protein, Hb: Hemoglobin, Htc: Hematocrit, WBC: White blood cell, PLT: Platelets, MPV: Mean platelet volume, RDW: Red cell distribution width, Neut: Neutrophil, Lym: Lymphocytes, NLR: Neutrophil lymphocytes ration, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BP: Blood pressure, DVT: Deep vein thrombosis, DM: Diabetes mellitus, HTN: Hypertension, CRF: Chronic renal failure, CAD: Coronary artery disease, CHF: Chronic heart failure, COAD: Chronic obstructive airway disease, NOAC: Novel oral anticoagulants, LMWH: Low-molecular-weight heparin.

Table 2. Echocardiographic variables and clinical outcomes of the study population

Parameters	All patients (n= 203)	TAPSE/sPAP <0.494 (n= 114)	TAPSE/sPAP >0.494 (n= 89)	p value
TAPSE	19 (16-22)	17 (14-20)	21 (19-24)	**<0.001**
sPAP	40 (30-60)	56 (45-65)	30 (30-35)	**<0.001**
TR				
0	8 (3.9)	1 (0.9)	7 (7.9)[a]	
1	87 (42.9)	16 (14.0)	71 (79.8)[a]	**<0.001**
2	33 (16.3)	26 (22.8)	7 (7.9)[b]	
3	51 (25.1)	48 (42.1)	3 (3.4)[b]	
4	24 (11.8)	23 (20.2)	1 (1.1)[b]	
RV diameter	38 (33-42)	41 (37-45)	34 (29-38)	**<0.001**
LV ED diameter	45 (41-48)	44 (40-46)	46 (43-50)	**<0.001**
RV/LV ratio	0.83 (0.72-0.97)	0.93 (0.83-1.07)	0.74 (0.63-0.82)	**<0.001**
LVEF	60 (60-65)	60 (60-60)	60 (60-65)	**0.013**
LVDD				
None	95 (46.8)	53 (46.8)	42 (47.2)	
Grade 1	100 (49.3)	57 (50.0)	43 (48.3)	0.921
Grade 2	8 (3.9)	4 (3.5)	4 (4.5)	
MR				
0	116 (57.1)	61 (53.5)	55 (61.8)	
1	72 (35.5)	41 (36.0)	31 (34.8)	0.053
2	13 (6.4)	10 (8.8)	3 (3.4)	
3	2 (1.0)	2 (1.8)	0 (0)	
RA diameter	40 (34-45)	44 (38-50)	35 (31-40)	**<0.001**
PESI score	87 (64-109)	107 (90-118)	65 (50-75)	**<0.001**
PESI group				
1	55 (27.1)	10 (8.8)	45 (50.6)[a]	
2	42 (20.7)	12 (10.5)	30 (33.7)[a]	
3	42 (20.7)	30 (26.3)	12 (13.5)[b]	**<0.001**
4	42 (20.7)	40 (35.1)	2 (2.2)[b]	
5	22 (10.8)	22 (19.3)	0 (0)[b]	
In-hospital mortality	5 (2.5)	5 (4.4)	0 (0)	**0.045**
30-day mortality	8 (3.9)	8 (7.0)	0 (0)	**0.009**
Primary outcomes	40 (19.7)	40 (35.1)	0 (0)	**<0.001**
TAPSE/sPAP	0.454 (0.290-0.666)	0.312 (0.220-0.391)	0.700 (0.600-0.829)	**<0.001**

[a]= Significantly higher than group 1, [b]= Significantly lower than group 1.

TAPSE: Tricuspid annular plane systolic excursion, sPAP: Systolic pulmonary arterial pressure, TR: Tricuspid regurgitation, RV: Right ventricle, LV ED: Left ventricle and diastolic diameter, LVEF: Left ventricular ejection fraction, LVDD; Left ventricular diastolic dysfunction, MR: Mitral regurgitation, RA: Right atrium, PESI: Pulmonary embolism severity index.

RESULTS

The baseline clinical and demographic variables of the study population are given in Table 1.

ROC curve analysis was conducted to determine the optimal TAPSE/sPAP ratio cut-off value to indicate 30-day mortality. The highest combined sensitivity and specificity values crossed the curve at 0.494 (sensitivity= 100.0%; specificity= 45.6%) for 30-day mortality. The area under the curve was 0.763 (95% CI= 0.628-0.899; p= 0.012). The study population was divided into two groups according to the TAPSE/sPAP ratio. The mean age (60.77 ± 14.92 vs. 53.18 ± 15.39 years, p< 0.001), troponin [39 (10-106); 10 (1-23), p< 0.001], RDW [13.9 (13.0-15.7) vs. 12.9% (12.4-13.8), p< 0.001], ALT [22 (15-45) vs. 17 U/L (13-30), p= 0.024], creatinine [0.9 (0.8-1.1) vs. 0.8 mg/dL (0.7-1.0), p= 0.024], urea [17 (13-24) vs. 14 mg/dL (11-19), p= 0.005] heart rate [103 (87-114) vs. 89 bpm (78-100), p< 0.001] were lower in

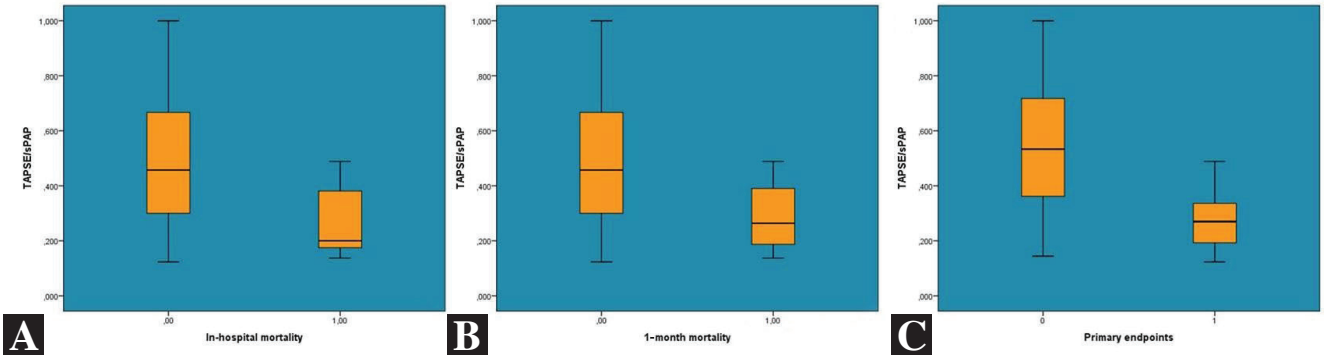

Figure 2. The TAPSE/sPAP ratios for patients with and without in-hospital mortality **(A)**, 30-day mortality **(B)** and primary endpoints **(C)**.

group 2 than group 1. CRP level [21.1 (11.0-42.8) vs. 36.8 mg/L (13.6-75.0), p= 0.025], systolic blood pressure [120 (95-135) vs. 130 mmHg (120-140), p= 0.001], diastolic blood pressure [70.5 (60-80) vs. 80 mmHg (70-87), p= 0.004], oxygen saturation [89 (87-94) vs. 96% (94-97), p< 0.001], fever [36.3 (36.1-36.5) vs. 36.4 (36.1-36.6) 0, p= 0.021] were higher in group 2. The incidence of hypotension [17 (14.9%) vs. 0, p< 0.001], mental disorder [7 (6.1%) vs. 0, p= 0.016], diabetes mellitus (DM) [34 (29.8%) vs. 13 (14.6%), p= 0.011], heart failure (HF) [18 (15.8%) vs. 2 (2.2%), p= 0.001], thrombolytic therapy [30 (26.3%) vs. 0, p< 0.001] were lower in group 2 while anticoagulant therapy [84 (73.7%) vs. 79 (88.8%), p= 0.007] was higher in group 2.

The echocardiographic variables and adverse clinical events are demonstrated in Table 2. TAPSE [17 (14-20) vs. 21 mm (19-24), p< 0.001], LVEDD [44 (40-46) vs. 46 mm (43-50), p< 0.001], LVEF [60 (60-60) vs. 60% (60-65), p= 0.013] were higher in group 2 compared to group 1. sPAP [56 (45-65) vs. 30 mmHg (30-35), p< 0.001], RV diameter [41 (37-45) vs. 34 (29-38) mm, p< 0.001], RV/LV ratio [0.93 (0.83-1.07) vs. 0.74 (0.63-0.82), p< 0.001], RA diameter [44 (38-50) vs. 35 (31-40) mm, p< 0.001], PESI score [107 (90-118) vs. 65 (50-75), p< 0.001] were higher in group 1. The incidence of in-hospital mortality [5 (4.4 vs. 0%, p= 0.045], 30-day mortality [8 (7.0%) vs. 0, p= 0.009] and primary adverse outcomes [40 (35.1 vs. 0%, p< 0.001] were higher in group 1. Additionally, the incidence of moderate to severe TR was higher in group 1.

Patients with in-hospital mortality had a higher PESI score [87 (64-108) vs. 119 (108-152), p= 0.006] and a lower TAPSE/sPAP ratio [0.457 (0.300-0.667) vs. 0.200 (0.175-0.381), p= 0.031] compared to those without mortality (Figure 2A). Patients with 30-day mortality also had a higher PESI score [86 (63-108) vs. 117 (108-139), p= 0.003] and a lower TAPSE/sPAP ratio [0.457 (0.300-0.667) vs. 0.264 (0.188-0.390), p= 0.012] (Figure 2B) compared to those without mortality. Furthermore, patients who met the primary endpoints had a higher PESI score [75 (59-98) vs. 125 (114-145), p< 0.001] and a lower TAPSE/sPAP ratio [0.533 (0.361-0.720) vs. 0.270 (0.193-0.336), p< 0.001] (Figure 2C) compared to those without mortality (Table 3). Patients with higher PESI scores exhibited lower TAPSE/sPAP ratios, with values of 0.667 (0.514-0.800) for low PESI scores, 0.433 (0.356-0.533) for intermediate PESI scores, and 0.264 (0.200-0.336) for high PESI scores, respectively (p< 0.001) (Table 4).

The correlation between the TAPSE/sPAP ratio and clinical variables is demonstrated in Table 5. The TAPSE/sPAP ratio was negatively correlated with PESI (r= -0.716, p< 0.001) (Figure 3), troponin (r= -0.490, p< 0.001), RDW (r= -0.307, p< 0.001), urea (r= -0.266, p< 0.001), heart rate (r= -0.355, p< 0.001), respiratory rate (r= -0.253, p< 0.001), RV diameter (r= -0.540, p< 0.001), RV/LV ratio (r= -0.590, p< 0.001), 176 RA diameter (r= -0.558, p< 0.001) and age (r= -0.298, p< 0.001). The TAPSE/sPAP ratio was positively correlated with systolic blood pressure (r= 0.275, p= 0.001), diastolic blood pressure (r= 0.227, p< 0.001), 178 saturation O_2 (r= 0.638, p< 0.001), fewer (r= 0.158, p= 0.024), LVEDD (r= 0.325, p< 0.001) and LV EF (r= 0.230, p= 0.001).

The multivariate logistic regression analyses revealed that the TAPSE/sPAP ratio [OR= 0.001, 95% CI= 0.000-0.476, p= 0.028] was an independent predictor of 30-day mortality in APE.

The TAPSE/sPAP ratio [OR= 0.009, 95% CI= 0.000-0.972, p= 0.049], PESI score [OR= 1.090, 95% CI= 1.050-1.132, p< 0.001], and HT [OR= 4.864, 95% CI= 1.381-17.138, p= 0.014] were also independent predictors of primary composite outcomes (Table 6). In simple linear regression analysis the TAPSE/sPAP ratio was found to be associated with the PESI score with (adjusted R^2= 0.425, ANOVA p< 0.001) statistical significance (PESI= -96.20 × TAPSE/sPAP + 134.992) (Figure 3). ROC curve analysis was conducted to determine the optimal TAPSE, sPAP, and TAPSE/sPAP ratio cut-off values to

Table 3. Comparison of TAPSE/sPAP ratio and PESI score in patients with and without adverse clinical events

Parameters	All patients (n= 203)	In-hospital mortality - (n= 198)	In-hospital mortality + (n= 5)	p value
TAPSE	19 (16-22)	19 (16-22)	14 (11-16)	0.051
sPAP	40 (30-60)	40 (30-60)	45 (45-80)	0.088
TAPSE/sPAP	0.454 (0.290-0.666)	0.457 (0.300-0.667)	0.200 (0.175-0.381)	**0.031**
PESI	87 (64-109)	87 (64-108)	119 (108-152)	**0.006**
		1-month mortality – (n= 195)	**1-month mortality + (n= 8)**	**p**
TAPSE	19 (16-22)	19 (16-22)	15 (12-19)	**0.040**
sPAP	40 (30-60)	40 (30-60)	53 (45-70)	**0.036**
TAPSE/sPAP	0.454 (0.290-0.666)	0.457 (0.300-0.667)	0.264 (0.188-0.390)	**0.012**
PESI	87 (64-109)	86 (63-108)	117 (108-139)	**0.003**
		Primary composite endpoints – (n= 163)	**Primary composite endpoints + (n= 40)**	**p**
TAPSE	19 (16-22)	20 (17-22)	15 (12-19)	**<0.001**
sPAP	40 (30-60)	35 (30-55)	60 (50-70)	**<0.001**
TAPSE/sPAP	0.454 (0.290-0.666)	0.533 (0.361-0.720)	0.270 (0.193-0.336)	**<0.001**
PESI	87 (64-109)	75 (59-98)	125 (114-145)	**<0.001**

TAPSE: Tricuspid annular plane systolic excursion, sPAP: Systolic pulmonary arterial pressure, PESI: Pulmonary embolism severity index.

Table 4. The association between TAPSE/sPAP ratio and PESI score

Parameters	PESI low (1-2) (n= 97)	PESI intermediate (3) (n= 42)	PESI high (4-5) (n= 64)	p value
TAPSE	20 (18-23)	19 (17-21)	16 (13-19)[a,b]	<0.001
sPAP	30 (30-37)	45 (35-55)[c]	60 (50-74)[c,d]	<0.001
TAPSE/sPAP	0.667 (0.514-0.800)	0.433 (0.356-0.533)[a]	0.264 (0.200-0.336)[a,b]	<0.001

[a]= Significantly lower than group 1, [b]= Significantly lower than group 2, [c]= Significantly higher than group 1, [d]= Significantly higher than group 2.
TAPSE: Tricuspid annular plane systolic excursion, sPAP: Systolic pulmonary arterial pressure, PESI: Pulmonary embolism severity index.

indicate 30-day mortality and primary adverse outcomes. In the 30-day mortality analyses, the highest combined sensitivity and specificity values crossed the curve at 14.5 (sensitivity= 50.0%; specificity= 83.6%) for TAPSE. The area under the curve was 0.714 (95% CI= 0.530-0.898; p= 0.040). The highest combined sensitivity and specificity values crossed the curve at 41 (sensitivity= 100.0%; specificity= 54.4%) for sPAP. The area under the curve was 0.717 (95% CI= 0.597-0.837; p= 0.038). The highest combined sensitivity and specificity values crossed the curve at 0.494 (sensitivity= 100.0%; specificity= 45.6%) for TAPSE/sPAP ratio (Figure 4A) The area under the curve was 0.763 (95% CI= 0.628-0.899; p= 0.012). In the primary outcomes analyses, the highest combined sensitivity and specificity values crossed the curve at 15.5 (sensitivity= 52.2%; specificity= 85.9%) for TAPSE. The area under the curve was 0.749 (95% CI= 0.660-0.838; p< 0.01). The highest combined sensitivity and specificity values crossed the curve at 49 (sensitivity= 85.0%; specificity= 71.8%) for sPAP. The area under the curve was 0.811 (95% CI= 0.752-0.870; p< 0.001). The highest combined sensitivity and specificity values crossed the curve at 0.387 (sensitivity= 92.5%; specificity= 70.6%) for the TAPSE/sPAP ratio (Figure 4B). The area under the curve was 0.855 (95% CI= 0.804-0.907; p< 0.001).

DISCUSSION

In our study, it was demonstrated that impaired TAPSE/sPAP ratio was a strong predictor of in-hospital and 30-day mortality in acute pulmonary embolism. Additionally, it was associated with adverse cardiovascular outcomes. We also revealed that the TAPSE/sPAP ratio was negatively correlated with the PESI score. To the best of our knowledge, this is the first study to compare the correlation of TAPSE/sPAP ratio with PESI score in patients with APE.

Table 5. The correlation between TAPSE/sPAP ratio and clinical variables

Parameters	Correlation coefficient	p value
PESI	-0.716	**<0.001**
Hs-Troponin I	-0.490	**<0.001**
RDW	-0.307	**<0.001**
Urea	-0.266	**<0.001**
Systolic BP	0.275	**0.001**
Diastolic BP	0.227	**<0.001**
Heart rate	-0.355	**<0.001**
Pulse O_2 saturation	0.638	**<0.001**
Respiratory rate	-0.253	**<0.001**
Fever	0.158	**0.024**
RV diameter	-0.540	**<0.001**
LV ED diameter	0.325	**<0.001**
RV/LV ratio	-0.590	**<0.001**
LV EF	0.230	**0.001**
RA diameter	-0.558	**<0.001**
Age	-0.298	**<0.001**

RCW: Red cell distribution width, TAPSE: Tricuspid annular plane systolic excursion, sPAP: Systolic pulmonary arterial pressure, LV: Left ventricle, RV: Right ventricle, LV ED: Left ventricle and diastolic diameter, LVEF: Left ventricular ejection fraction, RA: Right atrium, PESI: Pulmonary embolism severity index, BP: Blood pressure.

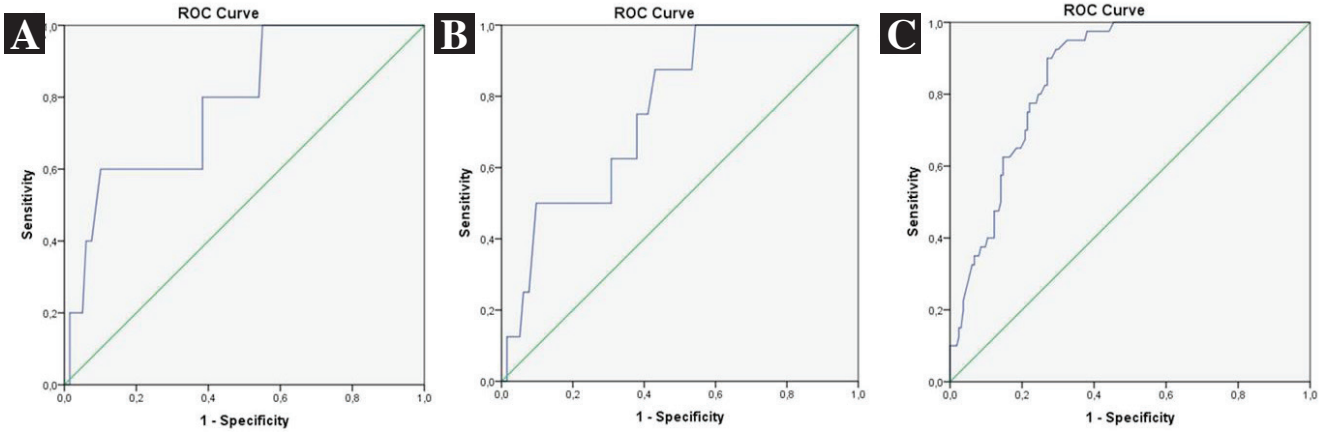

Figure 3. The correlation between TAPSE/sPAP ratio and PESI score.

While mortality is around 30% in patients with APE who are not properly diagnosed and treated, this rate ranges between 2% and 8% with early diagnosis and successful treatment[16]. For this reason, prognostic determination and choosing the right treatment for APE patients is a very important step. The RV function is of great importance in the prognostic evaluation of APE. The RV dysfunction detected in APE patients not only provides information on hypotension, cardiorespiratory deterioration and mortality that may develop, but also provides useful information on treatment selection[17,18]. TAPSE is an echocardiographic parameter that provides simple and rapid results in demonstrating right ventricular function. Previous studies have shown that TAPSE can be a physiological indicator of right ventricular systolic functions and is a method that can be used to evaluate right ventricular systolic function[19-21]. However, TAPSE alone provides only a longitudinal measurement and is insufficient to show global function[4]. Another parameter that determines the prognostic value of pulmonary embolism is pulmonary artery pressure[22]. The RV, normally working against a low afterload, causes physical occlusion of the pulmonary arteries, hypoxic vasoconstriction, and pulmonary artery vasoconstriction leading to increased resistance in the pulmonary vascular bed with RV afterload. As a result, increased pulmonary artery pressure makes it difficult for the RV to cope with this pressure load, and RV function is further impaired[23]. The TAPSE/sPAP

Table 6. Multivariate analysis giving information about independent predictors of 30-day mortality and primary composite endpoints

Parameters	Multivariate analysis		
	Odds ratio	**95% CI**	**p value**
TAPSE/sPAP	0.001	0.000-0.476	0.028
DM	1.628	0.260-10.193	0.603
HTN	1.211	0.221-6.625	0.826
WBC	1.038	0.914-1.179	0.567
Creatinine	4.202	0.737-23.971	0.106
Primary composite endpoints	**Odds ratio**	**95% CI**	**p**
Chronic renal failure	1.975	0.261-14.927	0.509
TAPSE/sPAP	0.009	0.000-0.972	0.049
PESI score	1.090	1.050-1.132	<0.001
Smoking	2.478	0.621-9.886	0.199
DM	2.076	0.480-8.984	0.329
HTN	4.864	1.381-17.138	0.014

TAPSE: Tricuspid annular plane systolic excursion, sPAP: Systolic pulmonary arterial pressure, DM: Diabetes mellitus, HTN: Hypertension, WBC: White blood cell, PESI: Pulmonary embolism severity index.

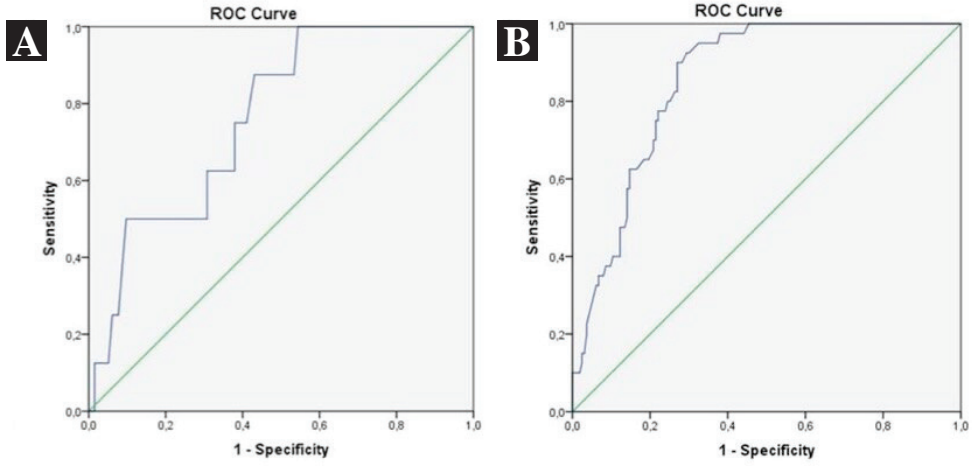

Figure 4. Receiver-operating characteristic curve indicating the discriminative ability of the TAPSE/sPAP ratio for 30-day mortality **(A)** and primary endpoints **(B)**.

ratio, calculated by these two important echocardiographic markers, provides valuable information about the global function of the RV[10,24].

The normal range for TAPSE/sPAP is typically between 0.8 and 1.8, and while these values may vary with age, they do not vary with gender[24]. Similarly, we did not see a difference between sexes in a disease state. A high ratio means the RV is functioning well given the afterload. The ratio will decrease as sPAP increases, when RV function estimated by TAPSE declines, or both[19,24,25].

The TAPSE/sPAP ratio has been associated with short-term outcomes in patients with APE in previous studies. In the study conducted by Lyhne et al., the TAPSE/sPAP ratio in low-risk APE patients was found to be 0.47 in patients with a primary endpoint of seven-day mortality and the need for invaluable treatment[12]. As a result of the data in this study, while TAPSE and TAPSE/sPAP ratio were predictive in seven-day mortality, sPAP alone was not significant. Interestingly, considering the 30-day mortality results of these patients, only the TAPSE/sPAP ratio was associated with this outcome[12]. As a result of the ROC curve analysis we conducted in our study, the predictive value of the TAPSE/sPAP ratio in APE patients was found to be 0.494. As such, it appears to be consistent with previous studies. In the present study, a low TAPSE/PASP ratio was found to be associated with in-hospital mortality, 30-day mortality, and primary outcomes that include hypotension, and thrombolytic treatment requirement. Besides these poor outcomes, the TAPSE/PASP ratio also had a relationship with

traditional parameters of determining the right heart such as RV diameter, RV/LV ratio, tricuspid regurgitation, right atrium diameter.

Although there are many parameters that determine the prognosis in patients with pulmonary embolism, the PESI score is the most commonly used tool as recommended by the guidelines[5]. This scoring, which was put into clinical practice more than 15 years ago, is used in two different ways as the traditional PESI, which includes 11 clinical variables[4], and the simplified PESI, calculated with six criteria[26]. The PESI score, which is classified into five different groups, is considered an important predictor of 30-day mortality in APE patients. Mortality predictions ranging from 1% to 10% can be made among these five groups[4,26]. Despite all these broad usage and recommendations, the PESI scoremay not be sufficient in terms of hemodynamic evaluation. It is especially weak in evaluating the right ventricular dysfunction caused by APE. For this reason, transthoracic echocardiographic evaluations have been routinely used in APE patients in recent years as they are easy to access, inexpensive and simple methods that can be applied at the bedside, and studies have shown that this evaluation has successful predictive effects[26]. In a study by Burgos et al., TAPSE and sPAP measurements added to the PESI score were found to be a better predictor of mortality than the PESI score alone in patients with APE[27]. Although not as strong as the PESI score, TAPSE and sPAP values separately gave predictive results in terms of one-month mortality. On the other hand, they revealed that the TAPSE/sPAP ratio can be an alternative assessment to PESI. Indeed, in the correlation analysis in our study, a strong negative correlation was found between the TAPSE/sPAP ratio and the PESI score ($r= -0.716$, $p< 0.001$). In addition, the TAPSE/sPAP ratio was determined as an independent predictor of 1- month mortality in patients with acute pulmonary embolism in multivariate analysis [OR= 0.001, 95% CI= 0.000-0.476, p= 0.028].

Another data supporting the results we obtained in our study is that PESI score parameters are correlated with the TAPSE/sPAP ratio even when evaluated separately. As a matter of fact, PESI score criteria such as age, high heart rate, low oxygen saturation, fever, hypotension, and mental status disorder were found to be significantly associated with a low TAPSE/sPAP ratio. The TAPSE/sPAP ratio was found to be as predictive as the PESI score in primary composite outcomes including hypotension, shock, mental status impairment, mechanical ventilator requirement, thrombolytic requirement, and death. As such, our results seem to be compatible with the study by Lyhne et al[12].

Limitations of the study

The main limitations of the study are that it is single-centered and retrospective, and the number of patients is relatively low. Furthermore, the fact that the echocardiographically measured TAPSE measurement is only an indicator of RV longitudinal systolic functions and not RV global functions is considered a limitation. Furthermore, it's important to note that the measured systolic pulmonary arterial pressures are calculated based on the tricuspid regurgitation (TR) jet using the modified Bernoulli's formula, and these pressures are not measured invasively, which are among the significant limitations of the study. The fact that the echoparameters measured in the pre-treatment echocardiographic evaluation at the first admission, which can sometimes end in shock or cardiac arrest, such as APE, cannot be performed by more than one person and reproducibly, also creates significant limitations.

CONCLUSION

We found that the TAPSE/sPAP ratio is an important indicator in determining the prognosis of patients with acute pulmonary embolism. However, we determined a strong negative correlation between the PESI score and the TAPSE/sPAP ratio used in line with the guidelines in APE prognosis.

Therefore, the TAPSE/sPAP ratio may be used as an alternative tool in determining the prognosis of APE patients as it is easily accessible, affordable, and effective.

Ethics Committee Approval: This study was approved by the İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Clinical Research Ethics Committee (Decision no: 10678112-514.10-03, Date: 11.02.2021).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

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