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Significance of pPTT-TAPSE and Mortality Prediction for Acute Pulmonary Thromboembolism in Emergency Department

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Aim: TAPSE and pPTT are new echocardiographic parameters recommended in the evaluation of right ventricular function. Examine the echocardiographic parameters of patients diagnosed with acute pulmonary thromboembolism and determine the predictive of mortality.
Materials and Methods: The study was prospectively. Patients diagnosed with PTE in the Emergency Department between 01.03.2019 and 31.12.2019 were included (86 patients (42 case - 44 control))in the study.
Results: pPTT mean scores of the case and control groups were 91.88 ms and 127,09 ms (p< 0,001). Also, the TAPSE mean scores were 1.76 mm and 2.60 mm for the case and control groups (p< 0,001). In terms of sPESI, 8 patients (19%) were determined to be at low risk in the case group. On the other hand, of the 34 patients (81%) in the case group determined to be at high risk, In the first 30 days after diagnosis, mortality developed in 2 patients (4.7%) in the case group. In the control group, the sPESI score of all participants was determined as low risk and no mortality developed (p <0.001). pPTT parameter was observed to be not at statistically significant levels to determine the predictive of mortality (AUC 0.194: p = 0.07). TAPSE parameter was observed to reach statistically significant levels of distinctive markers to determine the predictive of mortality (AUC 0.171: p = 0.05).
Conclusion: We recommend the determination of pPTT and TAPSE with acute PTE patients in emergency departments to predict mortality indicators and pulmonary pressure changes in the early period.

Keywords: Pulmonary Thromboembolism, TAPSE, pPTT, sPESI
Short Title in English: Significance and Mortality Prediction of pPTT-TAPSE

INTRODUCTION

Pulmonary thromboembolism (PTE) is a critical disease that is life-threatening and has high mortality when its diagnosis is delayed or not established. PTE causes nearly 300.000 deaths a year in Europe (1). Short-term mortality varies in a wide range between 2-95% depending on the severity of embolism (2). Mortality rates range from 1.7-15% even in non-high-risk PTE situations (3). Systolic and diastolic functions of the right ventricle (RV) have an important prognostic role in patients with cardiopulmonary disease. RV performance is sensitive to preload and changes in pulmonary pressure (4). Assessment of the effect on the RV in PTE is necessary for the clinician to determine the clinical decision of the disease and influence treatment decisions (5). To identify nonspecific signs and symptoms, several RV echocardiographic (Echo) parameters have been proposed practically. RV functions are impaired in PTE-related pulmonary hypertension (PH). Studies indicate that acute PTE increases the RV pressure in the lung, leading to dysfunction of the arterial system and RV and that it may progress in circulatory collapse with right heart failure (6).

Right heart failure is the most common cause of mortality in hospitalized Acute PTE patients and the main determinant of prognosis. European Society of Cardiology (ESC) guidelines recommended the assessment of RV function as a part of the clinical approach. Geometry-independent parameters such as Tricuspid Annular Plane Systolic Excursion (TAPSE) provide information about the RV function and can be used to overcome these limitations (4). Right ventricular ejection fraction (RVEF) is a marker of RV in PH, but its measurement is complex and time-consuming. TAPSE helps measure the longitudinal component of the RV contraction, and it is an easy measurement to obtain and reproduce (7). Studies have determined TAPSE significantly lower in patients with PTE, and particularly, this decrease was reported to be around 50% in the early PTE period (6,7,8,9).

Pulmonary Pulse Transit Time (pPTT) is a new parameter to evaluate heart functions (10). It is proportional to the pulmonary blood volume. Therefore, it can be used to measure pulmonary obstruction. pPTT was determined to be correlated with RV function and measurements of pulmonary vascular status (11). pPTT has recently been shown as a new echocardiographic marker by Wibmer et al. and has been reported to be used as an indicator of hemodynamic and vascular change in patients with pulmonary fibrosis and hypertension. It is a parameter that shows a negative correlation with pulmonary stiffness (12).

The Pulmonary Embolism Severity Index (PESI) has recently been found to be a highly reliable clinical prognostic model for Acute PTE patients. The PESI score was developed in 2005 with 11 parameters, but due to difficulties in remembering the PESI score and implementing it in crowded emergencies, it was reduced to the Simplified PESI (sPESI) in 2010 to include six of the 11 original PESI variables. Patients without variables (0 points) are classified as low risk, while variables between 1 and 6 (1-6 points) are classified as high risk

(13). Zwierzina et al. stated that PESI had a distinctive power in predicting short-term (30 days) mortality and morbidity in patients with acute pulmonary embolism. They reported that PESI and sPESI had similar accuracy and that sPESI was easier to use (14).

This study aimed to determine the relationship between echocardiographic parameters such as pPTT and TAPSE and Acute PTE patients and to investigate the usability of these parameters with sPESI scores as predictors of mortality.

METHODS

Study Group

The study group consisted of a total of 86 people, including 42 in the case and 44 in the control groups. The case group was made up of patients diagnosed with Acute PTE who did not have a disease that would affect pulmonary pressure. The control group was admitted to the emergency department with shortness of breath or chest pain, suspected PTE but diagnosed negative (35 myalgias, 5 gastritis, 3 anxiety, 1 mastodynia). It consisted of people with no additional disease and no lung or heart disease. As a result of the prior and post hoc power analysis, the sizes of the case and control groups planned for this study were observed to be adequate.

Exclusion Criteria

The exclusion criteria for the individuals included having any other pathological diagnosis other than PTE, malignancy, having other diseases that cause right heart loading (Chronic Obstructive Pulmonary Disease (COPD), Right Heart Failure, etc.), autoimmune and rhythm disorders, having a New York Heart Association (NYHA) functional status ≥ 2, acute or chronic kidney failure, pregnancy, and chronic systemic disease.

Data Collection

The study data were collected prospectively from individuals in the case and control groups between 01 March 2019 - 31 December 2019 with the institutional approval of Tokat State Hospital and the approval of the Ethics Committee with issue number 19-KAEK-251. For the diagnosis of Acute PTE of individuals in the case group, pulmonary CTA was done using the General Electric Revolution brand computerized tomography. The demographic characteristics (age, gender) of the patients and their medical file documents were recorded. The patients were administered an echo by a cardiology specialist physician using Vivid 7 (GE Medical System) brand echo device and measurements were recorded with the Modified Simpson Method. pPTT was defined as the time(at milliseconds) interval between the R-wave peak on the ECG and the corresponding peak late systolic pulmonary vein flow rate. TAPSE was evaluated by measuring the distance (in millimeters) of the last diastole to the last systole with the M-mode from the RV free wall in the same cardiac cycle.

Statistical Analysis

The Shapiro-Wilk test was employed to test if the data were normally distributed. Student's t-test was used to compare the properties that had normal distribution in 2 independent groups, and the Mann-Whitney U test was used to compare the properties without normal distribution in 2 independent groups. Relationship analyses of categorical variables observed in two independent groups were analyzed with Pearson and Exact Chi-Square tests. In the study, the effects of pPTT and TAPSE parameters on the dependent variable were analyzed with the Multivariate Logistic Regression method. Also, the receiver operating characteristic (ROC) analysis was conducted to calculate the power of pPTT and TAPSE parameters in predicting the dependent variable. Descriptive statistics included mean ± standard deviation values for quantitative variables, and frequency and % values for categorical variables. SPSS Windows

Version 22.0 software package was used for statistical analysis, and statistical significance was considered as $p < 0.05$

RESULTS

The examination of the mean age in the case and control groups indicated that the mean age of the patients in the case group (66.90 ± 17.10) yielded statistically significantly higher values compared to the mean age of the individuals in the control group (50.00 ± 14.96) ($p < 0.001$). On the other hand, the evaluation of the mean pPTT in the case and control groups revealed that the mean pPTT of the individuals in the control group (127.09 ± 4.83ms) yielded statistically significantly higher values compared to the mean pPTT of the individuals in the case group (91.88 ± 18.81ms) ($p < 0.001$). Similarly, the examination of the mean TAPSE value in the case and control groups showed that the mean TAPSE value of the individuals in the control group (2.60 ± 0.18 mm) was statistically significantly higher compared to that of the individuals in the case group (1.76 ± 0.53 mm) ($p < 0.001$). No statistically significant differences were found between the case and the control groups in terms of gender ($p = 0.2$).

A statistically significant difference was observed in the case and control groups in terms of sPESI evaluation ($p < 0.001$). According to the sPESI evaluation, all of the observations in the control group were in the low-risk group (100%), and a 19.0% low-risk observation rate was found in the case group. Also, some individuals in the case group were observed to match sPESI high risk (1 point, 2 points, and 3 points) values. There were no statistical differences in terms of mortality rates of observations in the case and control groups ($p = 0.1$). The demographic characteristics of the case and control groups are shown in Table 1.

Table 2 presents the contribution of the variables pPTT and TAPSE, which were candidate variables that showed significant differences compared to the controls, using the Enter method in the multiple logistic regression model for the diagnosis of PTE. According to these results, the pPTT parameter was observed to be a statistically significant variable for PTE disease (OR: 0.55: p = 0.01). On the other hand, the TAPSE parameter was found to be not a variable that had a statistical significance for PTE disease (OR: 5,04: p = 0,08).

pPTT and TAPSE parameters, which are candidates for PTE diagnosis, were analyzed by ROC (Receiver operating characteristic) analysis in Table 3. For the PTE diagnosis, the Area-Under-the Curve (AUC) value of the pPTT parameter was observed to be statistically significant (AUC 0.01: p = 0.05). Otherwise, the AUC value of the TAPSE parameter was observed to not reach statistically significant levels for PTE disease (AUC 0.09: p = 0.17).

The contribution of the variables revealed using the Enter method in the multiple logistic regression model for the mortality estimation of pPTT and TAPSE values were examined in Table 4. According to these results, the pPTT parameter was not a statistically significant variable on mortality (OR: 1.01: p = 0.85). In addition to this, the TAPSE parameter was observed to be not a variable that had a statistically significant effect in determining mortality, either (OR: 0.11: p = 0.25).

pPTT and TAPSE parameters, which are candidates for the diagnosis of mortality, were analyzed by ROC (Receiver operating characteristic) analysis in Table 5. The Area-Under-Curve value of the pPTT parameter was observed to be not at statistically significant levels (AUC 0.194: p = 0.07). On the other hand, the AUC value of the TAPSE parameter was observed to reach statistically significant levels of distinctive markers for mortality estimation (AUC 0.171: p = 0.05).

DISCUSSION

TAPSE provides direct information about RV systolic functions and has a good correlation with RVEF (15).TAPSE varies inversely with PTE and has been determined significantly lower in patients with PTE (6-7-8-9). According to the results of the study conducted by Şahan et al., TAPSE was found to be significantly higher in the group with an sPESI score <1 compared to the group with ≥1 (4). According to the results obtained from the present study, TAPSE values were found to be significantly lower in PTE patients in the case group compared to the control group, which was in parallel with the literature.

pPTT measurement is reproducible, and it is a measurement model that accurately reflects cardiopulmonary function. pPTT is defined as the transit time to pass from the pulmonary valve to the pulmonary veins, and it has been reported to decrease in PH. pPTT has also been shown to have a negative relationship with RV function and measurements of pulmonary vascular status and increased pulmonary pressure. In particular, according to the study of Brittain et al., a pPTT value of <105 ms was reported to be an indicator of the increase in the mean pulmonary artery pressure (11-16-17-18). According to the results of this study, the pPTT value was found to be significantly lower in case group patients. In line with this information, measuring pPTT and TAPSE values by doing Echo imaging in patients who have been diagnosed with PTE in the emergency department will reveal RV functions and facilitate patient management.

sPESI has been reported to have a distinctive power in predicting short-term morbidity and mortality in acute PTE patients (14). The sPESI low-risk group (0 points) was found to have a PTE-bound 30-day mortality rate as 0%, whereas the group with high risk ($\geq$1 point) was determined to have a 6.3% rate (15). According to the findings of this study, a difference was found between the case group and the control group sPESI scores. However, when the mortality rates were examined, a similarly significant difference was found. Accordingly, it can be said that the levels determined according to sPESI values for the mortality prediction of patients diagnosed with PTE in emergency departments should be examined.

For the diagnosis of PTE, pPTT was found to be correlated with pulmonary vascular status, therefore it is a significant parameter in terms of PTE risk (11-12-16-19). It is also closely related to diastolic and systolic cardiac functions (10). pPTT is a good predictor for right ventricular fractional area change (17). According to multiple logistic regression and ROC analysis results by the literature, the pPTT parameter is a significant marker for the detection of PTE disease.

While TAPSE is more strongly associated with pulmonary vascular resistance than with pre-PTE, the post-PTE correlation has not been found, meaning that it can be used for the diagnosis of PTE, its use after diagnosis is not significant (9). According to the multiple logistic regression and ROC analysis results, TAPSE value is not a significant predictor in terms of detecting PTE.

RV function is closely related to PH (20). pPTT has been proven to be an integral part of the initial assessment of right heart function, it is particularly valuable for predicting morbidity and mortality (21). Pulmonary artery stiffness has also been shown to predict mortality in PH patients. RV function is a strong prognostic factor and mortality marker in PH (16). According to multiple logistic regression and ROC analysis results are different from the literature and the pPTT parameter is not a significant predictor of mortality.

TAPSE is useful in the evaluation of RV function in patients with Acute PTE and is a high predictor of mortality (22). Low TAPSE may also be indicative of PTE prognosis (15). It plays an important role as a predictor of mortality in PTE patients. It has been shown to have a significant correlation with poor outcome in patients with PTE with low TAPSE (6). TAPSE value in PH is one of the strongest predictors of mortality (23). The results of the ROC analysis show that TAPSE value may be predictive for mortality by the literature. According to multiple logistic regression analysis results, it was not determined as a predictor in terms of mortality.

LIMITATIONS

This was a single-center study, so it made the present results weaker. Also, pulmonary pressures couldn’t be measured invasively; thence, the pulmonary hemodynamics couldn’t be determined exactly. The determination of pPTT was limited to the availability of pulmonary vein doppler signals. This study didn’t approach the influence of concurrent treatment on pPTT.

Both of the functional exercise capacity and the variability of pPTT during the respiratory cycle weren't assessed systematically. The Investigator of this study analyzing the echocardiograms wasn't blinded to the study hypothesis and the patients' medical histories. The effect of conduction disorders or arrhythmias on pPTT wasn't assessed. This study has a simple baseline determination at a single time point so it does not reflect the patient status over long periods. The age difference between the case and control groups may also have affected the results.

CONCLUSION

Echo can be done at the bedside, it is non-invasive, and that it is free from radiation are its advantages against Pulmonary CTA. We recommend right ventricle assessment with Echo in patients diagnosed with acute PTE in emergency services in cases where administration of CTA is difficult, pPTT and TAPSE measurements, which are among new parameters, and the determination of sPESI score to detect both mortality indicators and pulmonary pressure changes in the early period. Unnecessary CTA examinations can be prevented by combining PPTT and TAPSE parameters with PERC score, especially in patients who cannot undergo CTA.

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Table 1. Demographic Characteristics of the Case and Control Groups

		Case Mean ± sd (min. max.)	Control Mean ±sd (min. max.)	p
Age		66.90±17.10 (23.00 96.00)	50.00±14.96 (22.00 75.00)	<0.001
pPTT		91.88±18.81 (39.00 124.00)	127.09±4.83 (118.00 140.00)	<0.001
TAPSE		1.76±0.53 (0.90 3.00)	2.60±0.18 (2.10 2.90)	<0.001
PAP		45.38±13.30 (20.00 65.00)		
EF		54.88±9.59 (35.00 65.00)		
Gender n(%)	*male*	25 (59.5)	31 (70.5)	0.2
	female	17 (40.5)	13 (29.5)	
sPESI n(%)	*low risk*	8 (19.0)	44 (100.0)	
	1.Point	20 (47.6)	0 (0.0)	<0.001
	2.Point	10 (23.8)	0 (0.0)	
	3.Point	4 (9.5)	0 (0.0)	
Mortality n(%)	*alive*	36 (92.3)	0 (0.0)	0.1
	exitus	3 (7.7)	0 (0.0)	

EF: Ejection Fraction
PAP: Pulmonary Arterial Pressure
pPTT: Pulmonary Pulse Transit Time
TAPSE: Tricuspid Annular Plane Systolic Excursion

sPESI: Simplified Pulmonary Embolism Severity Index

Table 2 Multiple logistic regression model for PTE

Parameter	Odds ratio	95%CI	p
pPTT	0,55	(0,350 0,88)	0,01
TAPSE	5,04	(0,081 314,73)	0,08

pPTT: Pulmonary Pulse Transit Time
TAPSE: Tricuspid Annular Plane Systolic Excursion

Table 3. Roc analysis for PTE

	Cut-off	AUC	Std Error	Sensitivity	Specificity	p
pPTT	120,5	0,01	0,007	0,024	0,114	0,05
TAPSE	2,65	0,098	0,040	0,095	0,386	0,17

pPTT: Pulmonary Pulse Transit Time
TAPSE: Tricuspid Annular Plane Systolic Excursion

Table 4. Multiple logistic regression model for Mortality

Parameter	Odds ratio	95%CI	p
pPTT	1,01	(0,915 1,11)	0,85
TAPSE	0,11	(0,002 5,05)	0,25

pPTT: Pulmonary Pulse Transit Time
TAPSE: Tricuspid Annular Plane Systolic Excursion

Table 5.Determination of the relationship between mortality and the parameters by ROC analysis

	Cut-off	AUC	Sensitivity	Specificity	p
pPTT	104,0	0,194	0,33	0,35	0,07
TAPSE	1,96	0,171	0,35	0,35	0,05

pPTT: Pulmonary Pulse Transit Time
TAPSE: Tricuspid Annular Plane Systolic Excursion