Role of right/left ventricular diameter ratio in therapy selection for high and low intermediate-risk pulmonary embolism in the Emergency Department

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Abstract. Patients with intermediate-risk pulmonary embolism (PE) comprise a significant patient population. Computerized tomographic pulmonary angiography (CTPA) plays a crucial role in diagnosis and determining the prognosis. Right ventricular diameter/left ventricular diameter (RVD/LVD) ratio measured through CTPA provides insight into right ventricular overload. The aim of the present study was to determine the role of RVD/LVD ratio on decision of treatment between high and low intermediate-risk PE. A retrospective observational study was conducted between May 2018 and May 2022 on patients with intermediate-risk PE at the Emergency Department (ED) of a tertiary care hospital. The demographic information, risk factors, vital signs at presentation, laboratory data, CTPA images and treatment modality of the patients were obtained. RVD/LVD was calculated from the CTPA images. All-cause mortality at 24 h, 7 and 30 days were recorded. A total of 127 patients were included. In total, 52 (40.9%) patients were in the low-intermediate risk group, and 75 (59.1%) patients were in the intermediate-high risk group. A total of 54 patients were administered thrombolytic therapy while 73 patients were not. The mean RVD/LVD was 1.35±0.25 in patients who were administered thrombolytic therapy and 1.17±0.34 in those who were not. A significant association was identified between RVD/LVD and the administration of thrombolytic therapy (P<0.001). RVD/LVD and mortality were not significantly correlated (P=0.248). No significant association was found between the administration of thrombolytic therapy and mortality (P=0.569). RVD/LVD assessed through CTPA was found to be significantly decisive for administering thrombolytic therapy but not significantly predictive for mortality in intermediate-risk patients with PE presenting to the ED.

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Key words: right ventricular diameter/left ventricular diameter ratio, intermediate-risk pulmonary thromboembolism, therapeutic options, mortality, Emergency Department

Introduction

In acute pulmonary embolism (PE), hemodynamic stability and the burden on the right side of the heart determine the risk and management approach. Patients with right-sided heart overload and hemodynamic stability are traditionally classified as having intermediate-risk PE (1). Right-sided heart overload can be detected using echocardiography (ECHO), computerized tomographic pulmonary angiography (CTPA) imaging, blood markers [brain natriuretic peptide (BNP) or troponin], and/or electrocardiography (2).

The clinical outcome, risk categorization, and management of PE depend on acute right ventricular (RV) dysfunction, which is mostly a consequence of pathological derangement in the pulmonary vasculature (3). Acute RV pressure overload and the ensuing increased right ventricular diameter (RVD) due to PE can lead to myocardial damage and major complications, including premature death, even in patients with PE who initially present with normal blood pressure (4).

To provide appropriate treatment within a safe and reasonable timeframe, accurate diagnosis is crucial and CTPA is the gold standard for detection of PE, but especially in smaller community Emergency Departments (EDs) without these resources or when the transfer of a patient is unsafe, ECHO can be a vital option for diagnosis and safe treatment. Although ECHO appears to be more accessible and offers no risk of ionizing radiation with a repeatable, portable, and non-invasive manner, it is almost operator-dependent and needs appropriate training (5,6).

There are findings of RV dysfunction on CTPA imaging that are well-defined in the literature, but the RVD/left ventricular diameter (LVD) ratio is a robust marker of RV dysfunction and early death, which may justify its use for prognostification after PE (7,8). Using signs of RV disfunction in the decision-making process for the management of intermediate-risk patients remains controversial, as does the administration of thrombolytic therapy to intermediate-risk patients. Hence, the present study aimed to emphasize the role of the RVD/LVD ratio in decision-making for treatment of this highly 'grey' cohort of patients with PE.

Patients and methods

Patient cohort and study design. The present study was a retrospective single-center observational study conducted on 127 male and female patients aged between 19-91 years, with a mean age of 67.8±16.8 years, who presented to the ED of University of Health Sciences Ankara Dıskapı Yıldırım Beyazıt Training and Research Hospital (Ankara, Turkey) with PE between May 31, 2018 and May 31, 2022. The present study was approved (approval no. 140/23) by the Institutional Review Board of the University of Health Sciences Ankara Dıskapı Yıldırım Beyazıt Training and Research Hospital (Ankara, Turkey). A G*Power analysis, using SPSS (v.23.0; IBM Corp.) performed to determine the sample size prior to the study, estimated a total of 108 patients with at least 54 in each group to detect a difference of 0.25 in the RVD/LVD ratio between the groups with a power of 95% and α=0.05.

The inclusion criteria were as follows: A diagnosis of acute PE in patients ≥18 years of age, confirmed by CTPA imaging and stratified as intermediate risk. Intermediate risk was defined as hemodynamic stability on admission, with a systolic blood pressure (SBP) of at least 90 mmHg without hemodynamic support and RV overload findings on CTPA imaging, or an increased cardiac troponin level, according to hospital records. In addition, intermediate risk was sub-stratified as intermediate-high or intermediate-low risk according to the PE guidelines of the European Society of Cardiology (ESC) (1) by incorporating the Pulmonary Embolism Severity Index (PESI) scoring system. Low risk is defined as PESI class III/IV with or without evidence of RV disfunction on imaging (CTPA/ECHO) or an elevated RV biomarker (troponin or BNP), while high risk is defined as PESI class III/IV with imaging evidence of RVD on imaging (CTPA or ECHO), and an elevated RV biomarker (troponin or BNP) (2). The exclusion criteria were as follows: Pregnancy, referral to University of Health Sciences Ankara Dıskapı Yıldırım Beyazıt Training and Research Hospital or referred from University of Health Sciences Ankara Dıskapı Yıldırım Beyazıt Training and Research Hospital to another facility, high-risk PE, intermediate-risk PE with missing medical data, no optimally measured RVD and/or LVD on CTPA images, and anatomical chest deformity.

Demographic characteristics, laboratory test results [troponin, proBNP, D-dimer, blood urea nitrogen (BUN), creatinine, white blood cell (WBC) count, hemoglobin (Hgb), platelet count, lactate], PESI, simplified PESI (sPESI) scores, RVD/LVD ratio and PE location from CTPA imaging, treatment modality (oral or parenteral anticoagulant, thrombolytic, surgical embolectomy, or direct thrombolysis via percutaneous catheter), hospitalization, and clinical outcome were recorded on previously prepared data forms. The patient data were accessed using a hospital automation system. Blood test results were obtained from the Emergency Biochemistry Laboratory of the University of Health Sciences Ankara Dıskapı Yıldırım Beyazıt Training and Research Hospital. Troponin values were recorded only as positive or negative because they were determined using different kits and measurement methods between 2018 and 2022.

Radiological measurements were performed by a radiologist, who was experienced in cardiovascular CT imaging using standard axial plane reconstructions and who was unaware of the study results. CTPA imaging was performed with the GE Healthcare G-Optima 660 (128 slices) device with intravenous iohexol administered to all patients as a contrast agent. Maximum RVD and LVD were determined by manually marking the maximum distance of the endocardial border of the right or left ventricle from the interventricular septum. The largest RVD and LVD values, which were usually obtained at different craniocaudal cardiac positions determined by the radiologist, were used for the analysis (Fig. 1).

Based on the treatment modality, the patients were categorized into the 'systemic thrombolysis' group and the 'other' (parenteral/oral conventional anticoagulation alone, surgical embolectomy, or direct thrombolysis via percutaneous catheter) group.

The primary outcome was all-cause mortality within the first 30 days after PE. PESI and sPESI scores were calculated as clinical prediction scores according to the 2019 PE guidelines of the ESC (1). Mortality time points were determined to be 24 h, 1-7, and 7-30 days.

Statistical analysis. Statistical analyses were performed using SPSS (v.23.0; IBM Corp.). Normality of continuous variables was determined using the Kolmogorov-Smirnov test, and skewness and kurtosis were used as ancillary descriptive statistics. All analyses were performed using non-parametric tests because the data were not normally distributed in at least one group for each dataset. Descriptive statistics included number (percentage) for categorical variables, and either mean ± standard deviation or median (minimum-maximum) for numerical variables. Differences between numerical variables in the two independent groups were determined using the Mann-Whitney U test. Comparison of the ratios between independent groups was performed using the χ^2 test. The statistical α significance level was set at $P<0.05$.

Results

There was a significant association between patients who were administered thrombolytic therapy and were in the intermediate-high risk group ($P<0.001$). The mean RVD/LVD ratio was 1.35±0.25 in patients who were administered thrombolytic therapy and 1.17±0.34 in those who were not. There was a significant association between a high RVD/LVD ratio and the administration of thrombolytic therapy ($P<0.001$). In addition, there was a similar significant association between both a high D-dimer level and admission to the intensive care unit, with the administration of thrombolytic therapy ($P<0.001$).

Table I. Comparison of treatment regimen and variables.

Characteristics	Thrombolytic therapy administered	Thrombolytic therapy not administered	P-value
Sex, n (%)			
Female	36 (66.7)	38 (52.1)	0.099
Male	18 (33.3)	35 (47.9)	
Age (years), mean ± standard deviation/median (min-max)	67±16.6/69.5 (21-88)	68.4±17/73 (19-91)	0.560[a]
Laboratory findings, n (%) or mean ± standard deviation/median (min-max)			
Troponin (+)	41 (75.9)	47 (64.4)	0.163[b]
BNP	5,858.3±8,732.1/ 2,165 (116-35,000)	7,996.2±10,560.2/ 2,290 (196-35,000)	0.466
D-dimer	8,044.5±5,992.5/ 6,810 (90-20,500)	4,046.8±3,654.2/ 2,843 (188-18,200)	<0.001
RVD/LVD	1.35±0.25/1.33 (0.88-1.96)	1.17±0.34/1.14 (0.63-2.74)	<0.001
BUN	47.9±27.7/38 (2-132)	42.6±20.8/38 (8-114)	0.636
Creatinine	1.39±1.1/1.18 (0.57-8.1)	1.08±0.36/0.99 (0.5-2.49)	0.038
WBC	11.7±4.31/11.17 (3,13-26)	10.71±5.83/9.8 (1-43)	0.063
Hgb	14.4±12.2/12.8 (8.7-101)	12.6±2.3/12.7 (7.3-17.1)	0.655
Platelets	200.8±80.7/183.5 (28-431)	247.9±95.2/235 (12-574)	0.002
Lactate	4.26±3.63/3.2 (1-19)	2.73±1.83/2.1 (0.7-9.5)	0.002
PESI	119±31.7/115.5 (60-212)	109.5±30.6/107 (40-203)	0.065
Risk group, n (%)			
Intermediate-low risk	13 (24.1)	39 (53.4)	0.001[b]
Intermediate-high risk	41 (75.9)	34 (46.6)	
Hospitalization, n (%)			
Intensive care unit	31 (57.4)	9 (12.3)	<0.001[b]
Ward	23 (42.6)	64 (87.7)	
Survival (days) mean ± standard deviation/median (min-max)	9±7/7 (0-20)	11±10/7 (1-29)	0.758[b]
Mortality			
Deceased	11 (20.4)	12 (16.4)	0.569[b]
Survived	43 (79.6)	61 (83.6)	

[a]Mann-Whitney-U test and [b]χ^2 test. BNP, brain natriuretic peptide; RVD, right ventricular diameter; LVD, left ventricular diameter; BUN, blood urea nitrogen; WBC, white blood cell; Hgb, haemoglobin; PESI, pulmonary embolism severity index.

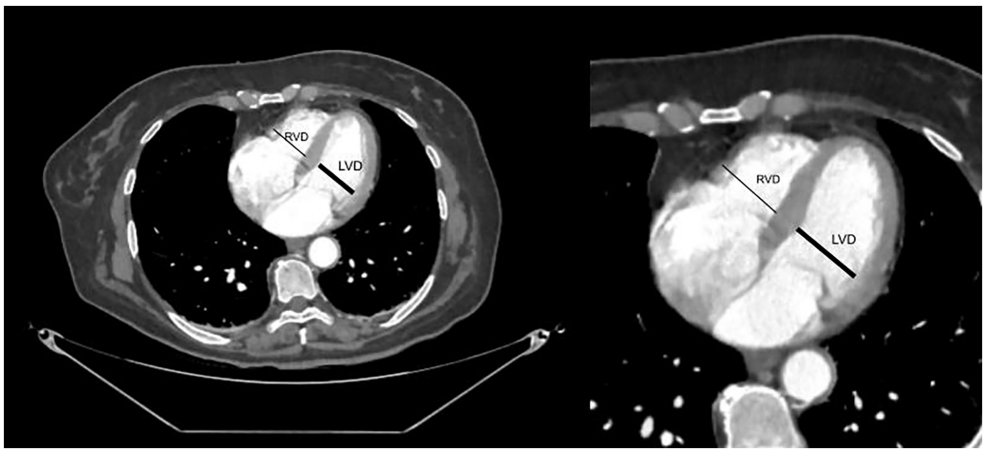

Figure 1. Measurement technique of RVD/LVD from the largest craniocaudal cardiac position. RVD, right ventricular diameter; LVD, left ventricular diameter.

Table II. Comparison of mortality and the variables.

Characteristics	Deceased	Survived	P-value
Sex, n (%)			0.780[b]
Female	14 (60.9)	60 (57.7)	
Male	9 (39.1)	44 (42.3)	
Age (years), mean ± standard deviation/median (min-max)	74.8±13.7/78 (36-90)	66.3±17.1/70 (19-91)	
Thrombolytic therapy, n (%)			0.569[a]
Administered	11 (47.8)	43 (41.3)	
Not administered	12 (52.2)	61 (58.7)	
Thrombolytic therapy, n (%)			0.126[a]
Positive	19 (82.6)	69 (66.3)	
Negative	4 (17.4)	35 (33.7)	
Laboratory results, mean ± standard deviation/median (min-max)			
BNP	4,157.3±4,566.1/ 2,100 (116-10,895)	7,123.5±10,053.6/ 2,260 (175-35,000)	0.509[a]
D-dimer	8,330.2±4,705.7/ 7,560 (1,221-20,500)	5,175.3±5,106.7/ 3,183.5 (90-20,300)	0.001[a]
RVD/LVD	1.32±0.32/1.21 (0.83-1.95)	1.23±0.32/1.2 (0.63-2.74)	0.248[a]
BUN	59.7±30.1/57 (23-132)	41.6±21.2/36.5 (2-121)	0.003[a]
Creatinine	1.32±0.54/1.3 (0.57-2.49)	1.19±0.82/1.04 (0.5-8.1)	0.102[a]
WBC	13.25±5.62/12.2 (5.13-26)	10.66±5.07/9.95 (1-43)	0.022[a]
Hgb	11.7±1.9/11.7 (8-15)	13.7±8.9/13 (7.3-101)	0.023[a]
Platelet	258.3±111.2/250 (95-574)	221.1±86.4/205.5 (12-492)	0.130[a]
Lactate	4.96±4.24/3.4 (0.7-19)	3.03±2.3/2.35 (1-17)	0.005[a]
PESI	137.1±31.4/131 (84-212)	108.4±29/105 (40-203)	<0.001[a]
Risk category, n (%)			0.109[b]
Low risk	6 (26.1)	46 (44.2)	
High risk	17 (73.9)	58 (55.8)	
Hospitalization, n (%)			0.001[b]
Intensive care unit	14 (60.9)	26 (25.0)	
Ward	9 (39.1)	78 (75.0)	

[a]Mann-Whitney-U test and [b]χ^2 test. BNP, brain natriuretic peptide; RVD, right ventricular diameter; LVD, left ventricular diameter; BUN, blood urea nitrogen; WBC, white blood cell; Hgb, haemoglobin; PESI, pulmonary embolism severity index.

Comparisons between demographic information, laboratory data, patient outcomes, patient risk groups, hospitalization status, and survival status by the treatment regimen are shown in Table I.

Mortality was significantly associated with higher D-dimer, BUN, lactate levels, WBC count, and a lower Hgb level (P=0.001, P=0.003, P=0.005, P=0.022 and P=0.023, respectively). A high PESI score was significantly correlated with mortality (P<0.001). Comparisons of demographic information, laboratory data, ED patient outcomes, patient risk groups, and hospitalization status by mortality status are presented in Table II.

When the sensitivity and specificity of the D-dimer level, RVD/LVD ratio and platelet count in predicting the requirement for thrombolytic treatment were evaluated by receiver operating curve (ROC) analysis, the cut-off values were determined as 4,394.5 for D-dimer (sensitivity, 66.7%; specificity, 71.2%), 1.21 for RVD/LVD ratio (sensitivity, 64.8%; specificity, 64.4%) and 214.00 for platelet count (sensitivity, 37%; specificity, 39.7%) (Fig. 2; Table III). Univariate and multivariate logistic regression analyses were both performed between the laboratory parameters of patients who were given thrombolytics and those who were not. D-dimer, platelet and RVD/LVD ratio were identified to be statistically significant and cut-off values were determined by logistic regression analysis (Table IV).

Discussion

Hemodynamic stability is the cornerstone of PE management, which is consistent with the results of the present study showing that intermediate-risk patients with a high RVD/LVD ratio were administered thrombolytic therapy. Beyond this,

Table III. Performances of variables in predicting the need for thrombolytic treatment.

	Area under the curve				
				Asymptotic 95% confidence interval	
Test result variable	Area	Std. error	Asymptotic sig.	Lower boundary	Upper boundary
D-dimer	0.725	0.046	0.000	0.635	0.814
RVD/LVD	0.698	0.046	0.000	0.607	0.788
Platelets	0.340	0.049	0.002	0.243	0.436

Std., standard; sig., significance; RVD, right ventricular diameter; LVD, left ventricular diameter.

Table IV. Logistic regression of variables in predicting the need for thrombolytic therapy.

	Univariate analysis				Multivariate analysis			
		95% CI				95% CI		
Parameter	OR	Lower boundary	Upper boundary	P-value	OR	Lower boundary	Upper boundary	P-value
RVD/LVD	3.33	1.595	6.950	0.001	3.084	1.364	6.970	0.007
D-dimer	4.952	2.317	10.585	<0.001	5.298	2.319	12.101	<0.001
Platelets	0.358	0.173	0.742	0.006	0.344	0.151	0.787	0.011

OR, odds ratio; CI, confidence interval; RVD/LVD, right ventricular diameter/left ventricular diameter.

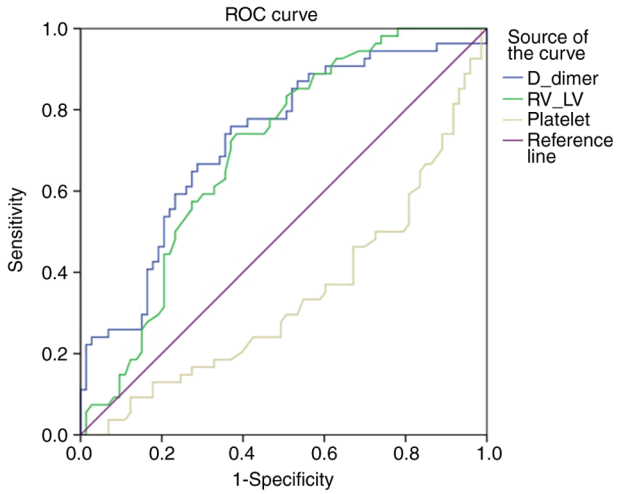

Figure 2. ROC curve of D-dimer, RVD/LVD and platelet count. ROC, receiver operating characteristic; RVD, right ventricular diameter; LVD, left ventricular diameter.

while the RVD/LVD ratio failed to predict 30-day mortality, a decision can be made regarding the therapeutic approach between low- and high-risk patients in the intermediate group. In this regard, PE severity and blood test results must also be considered. On CTPA images, assessment of the axial plane views is the gold standard and the most straightforward method to assess RV dysfunction because the images of the ventricular cavities are noticeably superior (9). Although the majority of patients with PE and assessed as intermediate-risk can be adequately treated with anticoagulants, a sizeable minority may deteriorate and necessitate reperfusion therapy (10), which is consistent with the results of the present study (Table I).

Thrombolytic therapy has several advantages over anticoagulant therapy alone, such as a more rapid elimination of thrombus material, and consequently, a more rapid reduction of pulmonary artery pressure and resistance, as well as a more rapid improvement of RV function (11). Therefore, particularly for patients at intermediate-high risk, there should be close monitoring, and reperfusion therapies should be considered in cases of hemodynamic deterioration, as reported in the ESC guidelines (1). One of the most important indicators of clot burden in the pulmonary arteries is the D-dimer level, where a higher value is associated with higher mortality and complications as a result of RV dysfunction (12). The mean D-dimer values of patients who received thrombolytic therapy were twice those who did not receive it, which is likely to be due to an increased afterload on the right ventricle and the consequences on hemodynamics (Table I). The areas under the ROC curves for the D-dimer level and the RVD/LVD ratio (Table III) represent the ability to distinguish between those who received thrombolytic therapy and those who did not. The proximity of the metrics indicated that the results for the RVD/LVD ratio and the D-dimer level were comparable. The areas under the ROC curve are close to each other but are not perfectly separated. According to these results, it is inferred that RVD/LVD ratio is not superior to D-dimer but can be combined synergistically as a diagnostic marker for thrombolytic therapy. However, the mode of therapy has been shown not to have prognostic

significance among high- and low-risk patient groups (12), as also observed in the present study.

In addition, the odds ratio for the RVD/LVD ratio (Table IV) indicates that an increase in the RVD/LVD ratio is associated with an increased likelihood of receiving thrombolytic therapy. The most commonly accepted thresholds for the RVD/LVD ratio on CT imaging are 0.9 and 1.0 and an increase in this ratio is a well-known indicator of RV dysfunction (13). An increased RVD/LVD ratio is associated with a concomitant LV filling defect and decreased cardiac output. It is an important indicator of the severity of PE accompanied by clinical findings such as hypotension, tachycardia, altered consciousness, syncope, chest pain due to decreased coronary circulation, and decreased urine output. It can be used as a surrogate for risk stratification in patients with acute PE, and aid in deciding a course of treatment (14). Given the findings of the present study it is considered that an increased RVD/LVD ratio can adequately stratify the risk for patients with a PE; therefore, this imaging modality can be used to assess patients with PE or individualize their treatment by means of disease severity assessment. In addition, the difference in the therapeutic approach between the high- and low-risk groups was associated with a higher risk of hemodynamic deterioration because patients at intermediate-high risk were at a higher level on the risk scale, as expected. Therefore, a treatment approach that considers RVD/LVD measurements on CTPA imaging without hemodynamic deterioration may guide ED physicians in decision-making, particularly when ultrasonography is unavailable (15,16).

Imaging plays an important role in the evaluation and management of acute PE and CTPA is the imaging modality of choice in the current standard of care (17,18). Beyond this, an ECHO is a dynamic evaluation tool for the assessment of RVD, tricuspid annular plane systolic excursion, RV systolic pressure, qualitative RV function, pulmonary hypertension, and McConnell's sign, although none of these can be used with absolute certainty in diagnosing PE, because some symptoms of RV dysfunction might manifest in the absence of PE as well as other cardiac conditions; but it is ideal for prognostication, identifying high-risk patients for urgent thrombolysis, monitoring medication response and ruling out other conditions. To evaluate patients with acute PE, CTPA and ECHO imaging have been employed in tandem as complementing technologies (18,19). In the present study, the RVD/LVD ratio was not compared with ECHO-derived parameters because it was retrospective in nature and ECHO findings for all patients could not be obtained, but the CT-derived parameters, particularly the RVD/LVD ratio is a promising measurement and an area of more recent focus.

The present study did not detect any significant association between the RVD/LVD ratio and mortality (P=0.248), which implies that the RVD/LVD ratio indicated the risk of hemodynamic deterioration and it can be a marker for the prevention of mortality. However, there was a significant association between a high PESI score, which calculates 30-day mortality in patients with PE, and mortality (P<0.001). Mortality can be accurately predicted using the PESI, particularly for those with a low score (20). In the ESC 2019 guidelines (1), patients are categorized into the intermediate-risk group instead of the low-risk group when they exhibit signs of RV failure, even though they do not have sufficiently high PESI and sPESI scores. Since PESI has such limitations, indicators of RV failure, such as the RVD/LVD ratio, can be used as ancillary parameters to support PESI.

The major limitation of the present study is the retrospective design. As there were multiple thrombi in all patients and a precise classification could not be performed, thrombus location was not considered. During the study, access to CT was periodically restricted due to the coronavirus 2019 outbreak, which meant that CTPA imaging could not be performed at the time of diagnosis in every patient, and this is likely to have resulted in deviations from the diagnostic algorithm. This, in turn, unfavourably affected the number of patients likely to be included in the study. Although the present study yielded results similar to those of other studies (13,14), it included a small number of patients, thus the results cannot be generalized. Beyond this, a lack of inter-rater reliability resulted in measurement bias. A different major limitation was that owing to the retrospective nature of the study, access to ECHO data from all patients was not possible and, therefore, the data could not be compared with the CTPA results. Prospective studies with larger sample sizes are required regarding the routine use of thrombolytic therapy in intermediate-risk patients and the role of the RVD/LVD ratio measured from CTPA imaging, as well as the use of cardiac ECHO in decision-making.

In conclusion, although the use of several parameters obtained from CTPA imaging to risk stratify patients with acute PE has been studied in detail previously, a definitive consensus has not yet been reached, warranting future studies on this subject.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

EK was responsible for conceptualization, investigation and writing the original draft. BMS was responsible for methodology, project administration, validation, visualization, supervision and editing the written draft. GÇ made substantial contributions to conception and design, acquisition of data, and the analysis and interpretation of data. İS performed data curation, wrote the original draft and was responsible for interpretation of the clinical data. İSD performed acquisition, analysis and interpretation of computer data. EK and İS confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were approved (approval no. 140/23) by the Institutional

Review Board of University of Health Sciences Ankara Dıskapı Yıldırım Beyazıt Training and Research Hospital (Ankara, Turkey) and were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Patient consent for publication

Informed consent was obtained from all individual participants included in the present study.

Competing interests

The authors declare that they have no competing interests.

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