Correlation of thrombosed vessel location and clot burden score with severity of disease and risk stratification in patients with acute pulmonary embolism

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Abstract

Objective: Computed tomography pulmonary angiography (CTPA) is used for the main diagnosis in acute pulmonary embolism (APE). Determining the thrombus location in the pulmonary vascular tree is also important for predicting disease severity. This study aimed to analyze the correlation of the thrombus location and the clot burden with the disease severity and the risk stratification in patients with APE.

Methods: The study included patients with APE diagnosed by CTPA who were admitted to the hospital between January 28, 2016, and July 1, 2019. Data collected were markers of severity in APE, including patient demographics, comorbidities, length of hospital stay, pulmonary embolism severity index (PESI) score, modified PESI score, Wells score, risk stratification according to the American Heart Association, systolic blood pressure (SBP), right ventricle diameter to left ventricle diameter ratio, pulmonary arterial pressure, brain natriuretic peptide, troponin, D-dimer, and plasma lactate levels, and vessel location of the thrombus, clot burden score, ratio of the pulmonary artery trunk diameter/aortic diameter, superior vena cava diameter (SVC) by CTPA, and survival. All parameters were analyzed in correlation with clot load and vessel location.

Results: Thrombus vascular location was found to be correlated with risk stratification and negatively correlated with SBP. Simplified Mastora score was correlated with risk stratification, SVC diameter, and D-dimer and negatively correlated with SBP. Occlusion of both the pulmonary artery trunk and any pulmonary artery with thrombus was associated with massive APE.

Conclusion: The level of the occluded vessel on CTPA may provide the ability to risk-stratify, and the clot burden score may be used for assessing both risk stratification and cardiac strain. *(Anatol J Cardiol 2020; 24: 247-53)*

Keywords: acute pulmonary embolism, clot burden, vessel

Introduction

Acute pulmonary embolism (APE), caused by the occlusion of the pulmonary arterial bed by a thrombus, is a life-threatening condition that has a high mortality rate of up to 14%–36% depending on the severity of the disease (1, 2). These early mortality rates can be reduced by 2%–10% with early diagnosis, risk stratification, and appropriate treatment (3). Therefore, determining the severity and conducting risk stratification of the disease as early as possible is important for deciding the treatment strategy, and it is defined as a criterion by the international guidelines (4). Computed tomography (CT) pulmonary angiography (CTPA) is widely used as a means of reaching the main diagnosis for APE, and it also plays an important role in determining the thrombus location in the pulmonary vascular tree, which is important for predicting disease severity. Occlusion of the main trunk or the right and left pulmonary artery suggests a higher risk than a peripheral occlusion, such as of the lobar and segmental arteries, as it would be expected that the pulmonary vascular bed is more affected in the former scenario. For this reason, some quantitative pulmonary clot burden scoring systems have been developed based on the thrombus location in the pulmonary vascular bed and the occlusion level (5, 6). These scores are calculated according to the thrombus location and the degree of vascular obstruction. Although a relationship has been observed between these scores and risk stratification, a relationship with clinical parameters indicating the disease severity and mortality are still under discussion, and the results are not consistent (7-9).

Many laboratory and clinical prognostic markers and scores have been developed for APE, such as risk stratifications, pulmonary embolism severity index (PESI) score (10), clinical parameters such as hypotension, the ratio of the right ventricle diameter

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to the left ventricle diameter (RV/LV ratio), superior vena cava (SVC) diameter (11), and troponin (12), brain natriuretic peptide (BNP) (13), and lactate levels (14). Recently, a study by Gul et al. (15) that investigated the correlation between the heart-type fatty acid-binding protein (H-FABP) and the clot burden score demonstrated that the H-FABP predicts 30-day mortality in APE and is a strong predictor of poor prognosis. To our knowledge, there are a limited number of studies in the literature that investigated the correlation of the thrombus location with the clinical and laboratory prognostic predictors, risk stratification, and survival. In the present study, the aim was to analyze the correlation between the thrombus location and the clot burden and parameters of severity and risk stratification in patients with APE.

Methods

Overall, 100 patients with APE were included in this single-center, retrospective cohort study, which was conducted in a University School of Medicine from January 28, 2016, to July 1, 2019.

This study was approved by the Local Ethics Committee of the University Hospital (Ankara-Turkey-02.07.2019.No:17-51). Ethical approval was in accordance with the Declaration of Helsinki.

Patients

The study included patients with a diagnosis of APE who were admitted to the hospital during the study period. The APE diagnosis was based on the pulmonary embolism (PE) protocol and a multidetector CTPA imaging study (4).

Exclusion criteria were patients undergoing thrombolytic or anticoagulant treatment at the time of APE diagnosis, unreliable APE diagnosis by CTPA, pregnancy, and age <18 years.

Data

The data were collected electronically from the hospital database and the patients' files and included patient demographics, comorbidities, length of stay in the hospital, PESI score, modified PESI score (mPESI), Wells score, risk stratification, systolic blood pressure (SBP), RV/LV ratio, and pulmonary arterial pressure (PAP) obtained noninvasively by an echocardiogram (ECHO), BNP, troponin, D-dimer, and plasma lactate levels, and CTPA findings, including thrombus vessel location, clot burden score, the ratio of the pulmonary artery trunk diameter/aortic diameter (PAt/AO), and SVC diameter. All data were evaluated within 24 h of admission. Survival time (days) was obtained from the government electronic mortality declaration system (www.obs.gov.tr). All of the patients' ID information was strictly protected.

Definitions

The thrombus vascular location was determined according to the most proximal arterial level occluded by thrombi seen in CTPA. For example, if the main pulmonary artery itself was thrombosed and/or any of its branches (right pulmonary artery or left pulmonary artery) were thrombosed, then it was defined as a pulmonary artery thrombus. The most proximal level of the thrombi in the lobar artery was defined as lobar artery thrombus and the most proximal level of the thrombi in the segmental artery were defined as segmental artery thrombus. The occluded artery levels were segmented from distal to proximal in three compartments as segmental, lobar, and pulmonary artery, respectively. Each CT angiogram was evaluated by a radiologist according to the usual clinical practice in which the evaluator was blinded to the patients' clinical presentations and laboratory outcomes (Fig. 1).

The clot burden of the PE was calculated according to the simplified Mastora score, which is based on the percentage of the occlusion ratio in the pulmonary arterial bed. It is a calculation in which the total score is obtained by determining the point value from 1 to 3 on a three point scale according to the percentage of obstruction area (1=<50% obstruction, 2=50%–99% obstruction, and 3=total obstruction) for each thrombus through the 31 arteries, including the five mediastinal, six lobar, and 20 segmental arteries. The maximal occlusion score of the summed values was 93 (Fig. 2) (5, 16).

The risk stratification of APE was determined according to the American Heart Association (AHA) guidelines (17). Subgroups of risk stratification were ranked as low-risk PE, submassive PE, and massive PE.

Statistical analysis

The data was collected from the files of the patients and the operating systems of the hospital and was analyzed using IBM SPSS Statistics Software for Windows v.23.0, IBM Corp., released 2015 (18). The normality of the variables was examined with the Shapiro-Wilk test, boxplots, and Q-Q plots. Descriptive statistics were shown as median, 25th and 75th percentiles as the normality assumption was not satisfied. Continuous variables with normal and homogeneous distribution were presented as mean value±standard deviation (SD). Furthermore, for continuous variables, the three independent groups were compared

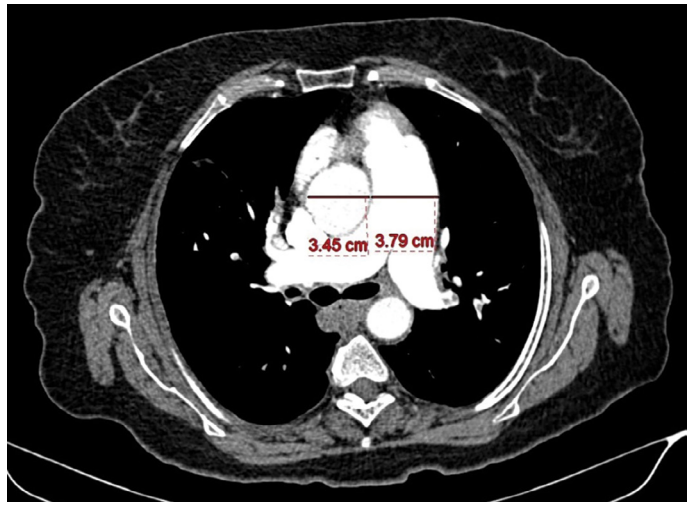

Figure 1. Measurement of aorta and pulmonary artery diameters

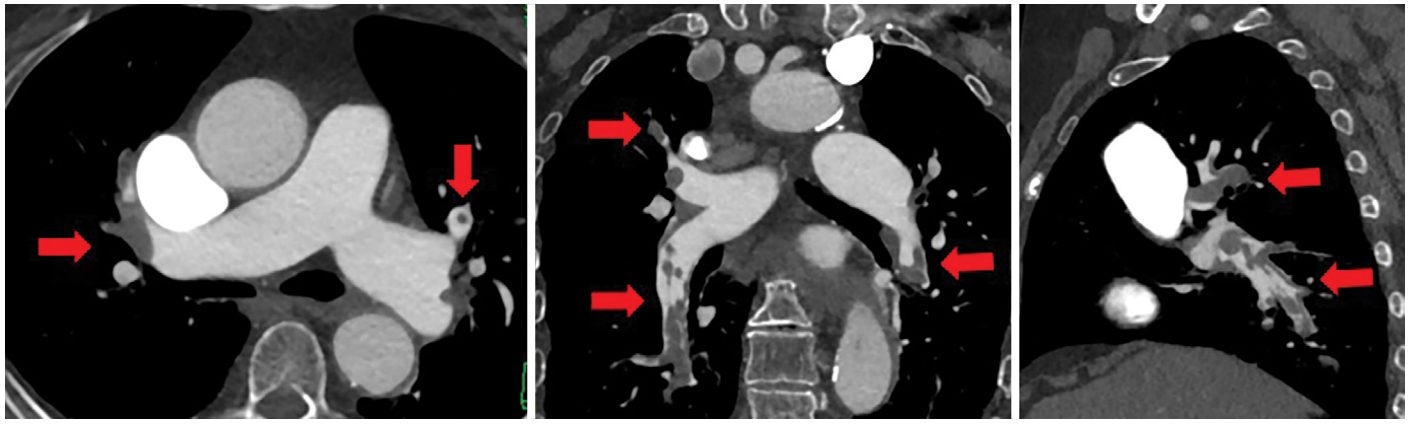

Figure 2. Axial, coronal, and sagittal multiplanar reformatted images demonstrate multiple pulmonary artery clots in the lobar and segmental pulmonary arteries (arrows) from two different patients with pulmonary thromboembolism. Axial computed tomography pulmonary angiography images show samples of point scales 1 (<50% pulmonary artery (PA) obstruction), 2 (50%–99% PA obstruction), and 3 (total obstruction) in left and right interlobar arteries (circles)

with the Kruskal-Wallis variance analysis, whereas categorical variables were compared with the chi-square test. Correlation of thrombus vascular location and the simplified Mastora score with the collected parameters and survival time were determined using Spearman's correlation coefficient (r). The level of statistical significance was set at p-value <0.05.

Results

Overall, 100 patients were included in the study; there were 58 females and 42 males (58% and 42%, respectively) with a mean age of 60±17 years. The most common comorbidities were malignancy (n=41, 41%), hypertension (n=37, 37%), and diabetes mellitus (n=11, 11%). The hospitalization time ranged from 0 to 60 days with a mean duration of 9.5±8.39 days and a median duration of 8 days. The demographic characteristics of the patients in the study are summarized in Table 1.

Correlation analysis of the thrombus vascular location and the simplified Mastora score with the research parameters are shown in Table 2. The thrombus vascular location was found to have a strong correlation with risk stratification and a negative correlation with SBP (r=0.36, p=0.01 and r=–0.26, p=0.009, respectively), but tended to weakly correlate with the PESI score and the PAP (r=0.172, p=0.088 and r=0.194, p=0.091, respectively). There was no correlation between the thrombus vascular location and survival or other clinical and laboratory parameters.

The simplified Mastora score was strongly correlated with risk stratification (r=0.491, p<0.001), PESI (r=0.234, p=0.021), PAP (r=0.363, p=0.001), PAt/AO ratio (r=0.282, p=0.004), SVC diameter (r=0.321, p=0.001), and D-dimer level (r=0.300, p=0.002) and negatively correlated with SBP (r=–0.300, p=0.022). However, there was no correlation between simplified Mastora score and the other parameters.

The thrombus location according to the risk groups and the analysis of the simplified Mastora score results are shown in Table 3. Both the main pulmonary artery and the bilateral (left and right pulmonary artery) thrombi had a significantly higher risk of being massive PTE (p<0.001 and p=0.011, respectively). In the low-risk group, lobar artery thrombi were more common (p=0.021). There was no correlation between the risk groups and the thrombi being unilaterally located. A bar graph showing the distribution of occluded vessel levels according to the risk groups is shown in Figure 3. The simplified Mastora score was found to show a statistically significant increase with risk among the groups (p<0.001).

Table 1. Demographic characteristics of the study patients

	All patients (n=100)
Gender, n (%)	
Female	42 (42)
Age, median (min–max)	63 (20-93)
Comorbidities, n (%)	
Asthma	6 (6)
COPD	8 (8)
Malignancy	41 (41)
Hypertension	37 (37)
Diabetes Mellitus	11 (11)
Heart failure	5 (5)
Atrial fibrillation	5 (5)
Coronary artery disease	9 (9)
Chronic renal failure	6 (6)
Dementia	8 (8)
Cerebrovascular event	3 (3)
Length of hospital admission (days), median (min–max)	8 (0-60)

COPD - chronic obstructive pulmonary disease

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Table 2. Correlation between level of occluded vessel and investigated parameters and survival time

	Level of occluded vessel (segmental/lobar/pulmonary artery)	Simplified Mastora score
PESI	r=0.172	r=0.234
	P=0.088	***P*=0.021**
mPESI	r=0.092	r=0.114
	P=0.351	*P*=0.242
Wells score	r=0.093	r=0.112
	P=0.361	*P*=0.253
Risk stratification	r=0.360	r=0.491
(low risk/submassive/massive)	***P*=0.012**	*P*<0.001
PAPs	r=0.194	r=0.363
	P=0.091	***P*=0.001**
RV/LV ratio	r=0.082	r=0.220
	P=0.534	*P*=0.100
BNP	r=0.031	r=0.112
	P=0.764	*P*=0.266
Troponin	r=0.132	r=0.114
	P=0.214	*P*=0.261
Lactate	r=0.116	r=-0.012
	P=0.303	*P*=0.914
D-dimer	r=0.127	r=0.300
	P=0.208	***P*=0.002**
SBP	r=-0.267	r=-0.300
	***P*=0.009**	***P*=0.022**
SVC diameter	r=0.123	r=0.321
	P=0.200	***P*=0.001**
PAt/AO ratio	r=0.100	r=0.282
	P=0.291	***P*=0.004**
Survival	r=0.163	r=0.021
	P=0.112	*P*=0.814

r is Spearman's correlation coefficient.
PESI - pulmonary embolism severity index, mPESI - modified pulmonary embolism severity index, PAP - pulmonary arterial pressure, RV/LV ratio - ratio of the right ventricle diameter to the left ventricle diameter, BNP - brain natriuretic peptide, SBP - systolic blood pressure, SVC - superior vena cava, PAt/AO - the ratio of the pulmonary artery trunk diameter/aorta diameter

Discussion

The primary findings of this study were that the location of the thrombus in the pulmonary artery tree in CTPA and the clot burden scores were positively correlated with the risk stratification according to AHA guidelines and negatively correlated with the SBP. No correlation was observed between the thrombus vessel location and established clinical and laboratory predictors of APE severity; on the other hand, thrombus burden score was correlated with PAP, D-dimer level, PAt/AO ratio, and SVC diameter. However, neither the thrombus location nor the clot burden score was found to be correlated with survival. This study is the first to investigate the correlation of the AHA-defined risk subgroups graded from low risk to massive embolism with the thrombus level and the clot burden score. The study also showed that central location was associated with massive APE and that the clot burden score increased with the rank in risk stratification. Although there are varying results reported in the literature, recent comprehensive studies have shown an association between thrombus location and risk stratification and prognosis (19, 20). In a recent meta-analysis, the emboli location in CTPA was associated with the risk stratification of the patients, conforming to our primary results. In the same meta-analysis, centrally located embolism was reported to be associated with a two-fold increase in mortality compared to ones distally located (19). In a similar study by Ghanima et al. (21), the emboli were stratified according to the pulmonary vascular tree in four groups of arteries, such as the subsegmental, segmental, lobar, and pulmonary artery. In their study, the researchers showed that the most proximal level of the thrombus in the vascular tree

Table 3. Comparison of occluded vessels and clot burden score among risk groups

Occlusion level	Massive APE (n=15)	Submassive APE (n=49)	Low risk APE (n=36)	*P* value*
Pulmonary artery, n (%)	14 (93.3)	26 (53)	11 (30.5)	***P*<0.001***
Lobar artery, n (%)	1 (6.6)	13 (26.5%)	16 (44.4)	**0.021***
Segmental artery, n (%)	0	10 (20.4)	9 (25)	0.100*
Occlusion side				
Right, n (%)	1 (6.6%)	9 (18.4)	7 (19.4)	**0.011***
Left, n (%)	0	4 (8.2)	10 (27.7)	
Bilateral, n (%)	14 (93.3)	36 (73.5)	19 (52.7)	
Clot burden score				
Simplified Mastora score, mean±SD	37.93±10.74	22.92±16.46	13.25±11.09	***P*<0.001**[Y]
Percentage of occlusion, mean±SD	40.7%±11.5	24.6±17.6	14.2±11.9	

*Chi-square test, [Y]Independent Samples Kruskal-Wallis test, SD - standard deviation

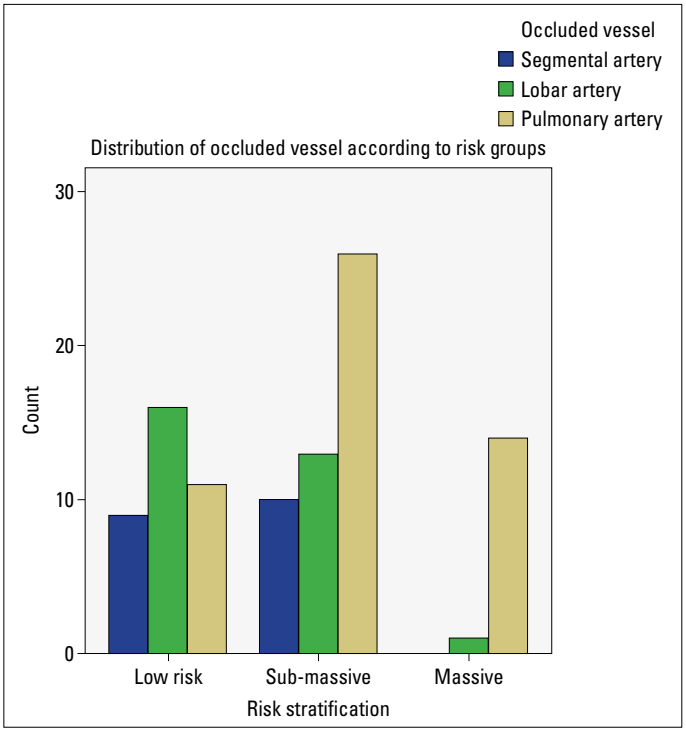

Figure 3. Distribution of occluded vessels according to risk groups

was associated with the APE severity. They stated that this classification may have a prognostic value for risk assessment (21).

There are different results as to whether the clot burden score is a definite factor for risk classification. Both Shen et al. (22) and Zhang et al. (23) showed that the clot burden score was significantly related to the high-risk group and was a determinant for this risk group in their studies. In our study, the mean clot burden score belonging to the high-risk group was lower, though its results broadly correlated to results of previous studies in the literature. This can be explained by the fact that we used a different classification system in our study. On the other hand, Lerche et al. (9) suggested that the clot burden score was not consistently distributed according to the risk group and could not be used in risk assessment. It is notable that with the results of this study, localization of the logged thrombus in CTPA and the clot burden score may have the potential to be used in the assessment of risk stratification.

Many markers and scoring systems, such as troponin, plasma lactate, D-dimer, BNP, RV/LV ratio, and PESI score, which have shown an association with disease severity and mortality in APE, are used as potential prognostic predictors for APE. Also, there is limited information on the utility of cardiovascular CTPA measurements, such as the PAt/AO ratio and SVC diameter. Presumably, pulmonary vessel obstruction by thrombus in APE may lead to pulmonary vascular resistance, pulmonary artery hypertension and dilatation, RV dysfunction, then heart failure, and finally death (24). Elevation in cardiac parameters, in particular troponin, BNP, and RV/LV ratio, are associated with RV dysfunction and are predictors of high risk; they also correlate with early mortality (12, 25, 26). In a recent study, a significant correlation was reported between mortality and SBP, RV/LV ratio, and SVC diameter. These parameters were determined to be risk factors for mortality (11). On the other hand, Beenen et al. (27) reported that RV/LV ratio, PAt/AO ratio, and SVC diameter in CTPA were not associated with short- and long-term mortality and were only found to be associated with a pulmonary artery (PA) trunk diameter >29 mm (27). There are studies demonstrating that BNP correlates with RV dilatation in CTPA, confirming its prognostic benefit (28-30). Increased plasma lactate levels are a well-known marker of the severity of tissue hypoxemia, which has been shown to be associated with short-term mortality that is independent of hemodynamic instability (30). D-dimer test screening is used in cases of suspected APE and D-dimer level is increasingly used as a prognostic marker; a positive correlation of D-dimer level with clot burden and RV dysfunction on CTPA was shown in a recent study (31). The PESI score can provide prognostic information in APE, particularly in identifying low-risk patients (10, 32).

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Recent studies have focused on the correlation between CTPA findings and these prognostic parameters of APE, but those reports are limited and the literature is not comprehensive. In our results, contrary to expectations, thrombus location did not correlate with laboratory value predictors of disease severity or clinical prediction score (Wells score), and there was no negative correlation with the survival time. The only strong negative correlation found was with SBP. These results were confirmed by several studies; Araoz et al. (8) reported in their study of 1193 PE patients that the RV/LV ratio and the embolism burden score were unrelated to short-term mortality but were associated with low SBP. Alonso Martinez et al. (20) found that SBP was significantly lower in central emboli than in peripheral emboli on CT. With our results, we would like to draw attention to the likely importance that the negative correlation of the occluded artery level and the clot burden score with SBP has in predicting hemodynamic impairment.

As shown in the present study, the clot burden score was correlated with more prognostic parameters than the thrombus vascular location. Additionally, the clot burden score showed no correlation with cardiac blood measurements other than D-dimer, Wells score, RV/LV ratio measured by ECHO, and survival time, but it was correlated with cardiovascular measurements such as SVC diameter and PAt/AO ratio in CTPA. This finding suggested that the clot burden score is also a valuable radiological measure to determine cardiac strain and disease severity. Ghuysen et al. (11) have similarly shown the correlation of the clot burden score with clinical severity ($r=0.380$, $p<0.001$) but not with mortality ($r=0.110$, $p=0.145$). Lerche et al. (9), with some similar supporting results, reported that the clot burden score was not correlated with clinical and laboratory predictors of APE severity, including troponin, blood pH, and Wells and Geneva scores. Other than that, it was weakly correlated with the serum lactate level (9). Furthermore, a meta-analysis reported that the clot burden score was not correlated with disease prognosis (19). Also, in a study by Abdelwahab et al. (33) in which the clot assessment was performed with regard to emboli location and clot volume, the results were in line with our results as it was found that the clot burden was strongly correlated with RV dysfunction findings in CTPA (PAt/AO ratio, $r=0.245$, $p=0.041$; SVC diameter, $r=0.287$, $p=0.016$) and was not correlated with PAP measured by ECHO ($r=0.239$, $p=0.173$) (33). On the other hand, both Ghanima et al. (21) and Zhou et al. (34) reported that the clot burden score was correlated with RV/LV ratio and troponin, which represents the severity of the LV dysfunction. Similarly, Shen et al. (22) categorized the patients in their study as high risk and non-high risk and furthermore reported that the RV/LV ratio was the determinant of high risk; the study also demonstrated that the RV/LV ratio showed a strong correlation with the clot burden score.

Study limitations

The important limitations of the study were that the study was retrospective in design and that it had a small sample size, and furthermore that the parameters investigated might have been influenced by many conditions other than PE. For instance, troponin and lactate may be affected by metabolic disorders, or BNP may be associated with underlying cardiac disorders. The lack of correlation between the clot burden and biomarkers may be because of underlying cofounders. However, a potential strength of the study is that it is the first study to investigate the correlation of ranked AHA risk stratification subgroups according to disease severity with occluded artery level and clot burden score in CTPA. The simplified Mastora score was preferred owing to the use of occlusion percentage in the calculation, as it is more current among the clot burden scoring systems.

Conclusion

In conclusion, the study determined that the AHA risk stratification correlates with both the clot burden score as well as with the occluded artery level; it also demonstrated that as the proximal obstruction level increases toward the center and as the clot burden increases, the risk and the hemodynamic deterioration increase. Therefore, the level of an occluded vessel on CTPA may provide the ability to rapidly risk-stratify patients with APE but might not be useful for prognostic prediction. Furthermore, the clot burden score may be used for assessing both risk stratification and cardiac strain.

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Peer-review: Externally peer-reviewed.

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