

## PROGNOSTIC ROLE OF CT PULMONARY ANGIOGRAPHY IN ACUTE PULMONARY EMBOLISM

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### ABSTRACT:

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**Background:** A growing number of studies in the last few years have searched for a potential prognostic role of MDCT to improve PE risk stratification. These studies were accompanied by puzzling details and heterogeneous results. Certain CT parameters have been nominated for this purpose. RV/LV ratio and arterial obstruction index were the most extensively studied parameters.

**Aim of our Study:** Is to investigate the prognostic role of CT pulmonary angiography in patients with acute pulmonary embolism.

**Patient and method:** 59 patients having severe or large sized acute PE diagnosed by CT angiography were followed through 30 days to 3 months for their short-term clinical outcome. Bad outcome indicators included: PE-related mortality, clinical deterioration and necessity for ICU aggressive treatment or thrombolytics. Patients CT prognostic parameters were assessed and statistically analyzed to determine their ability to predict major adverse outcomes of acute PE.

**Results:** Of all CT parameters, RV diameter was the best discriminator between adverse & non-adverse outcome groups in our study, comparable only to Mastora pulmonary artery obstruction score. It showed the highest negative predictive value 95.7% and a negative likelihood ratio very close to 0. RV diameter alone performed better than the commonly used RV/LV ratio as a measure of RVD in predicting PE adverse outcome. Septal bowing, substantial grades of IVC contrast reflux, PA & SVC diameters showed weak sensitivity & specificity results. A final logistic regression model combining three parameters (RV diameter + Mastora score + Age) was able to correctly define 83.9% of adverse outcome cases and 84.7% of overall cases in our study.

**Conclusion:** Our study supported the use of CTPA-derived indicators of right ventricular dysfunction and pulmonary artery obstruction scores as prognostic predictors in patients with acute PE.

**Key words:** CT Pulmonary Angiography; Pulmonary Embolism; Right Ventricular Dysfunction.

### INTRODUCTION:

Acute pulmonary embolism represents a major cardiovascular threat associated with a high short-term mortality rate of up to 50%

when left untreated, whereas treatment with anticoagulants decreases mortality to <5%<sup>(1)</sup>.

Rapid risk assessment in patients with acute PE is the key to select appropriate therapy. Patients estimated to be high risk of

PE-related morbidity and mortality should be considered for more intensive care settings and thrombolytic therapy or embolectomy, while patients with low risk are suitable for outpatient treatment<sup>(2)</sup>.

Prognostic models for risk stratification and identifying high-risk patients during acute PE therapy have been the main goal of recent studies. These models were based on clinical findings, echocardiography criteria, and cardiac biomarkers with various combinations<sup>(3)</sup>. For example, evidence has shown that right ventricular dysfunction (RVD), detected by echocardiography or biomarkers of myocardial strain (troponins or BNP), is a critical marker that may indicate a severe and possibly fatal PE and justify more aggressive treatment<sup>(4)</sup>. Pulmonary embolism severity index (PESI) & its simplified version (sPESI) is the most validated clinical prognostic score, out of its prognostic classes, PESI classes I and II (0–1.6 and 1.7–3.5% 30-day mortality risk respectively) or sPESI 0 (1.0% risk) allow the consideration of a patient with PE as being low-risk for 30-day mortality<sup>(2)</sup>.

CT pulmonary angiography is currently the gold standard frontline procedure for the diagnosis of PE. Additional to diagnosis, different CT pulmonary angiographic parameters have emerged in literature as “prognostic” tools for PE risk stratification<sup>(5)</sup>. Studied parameters include: right ventricular enlargement, increased RV/LV ratio, interventricular septal deviation, IVC or azygos contrast reflux, pulmonary artery diameter, emboli location, and several scores and indices for clot burden and distribution.

Although still no consensus has been reached regarding their performance, these CTPA-derived findings are promising and can be useful in stratifying prognosis for patients with acute PE.

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## **AIM OF THE WORK:**

The purpose of this work is to investigate the prognostic role of CT pulmonary

angiography in patients with acute pulmonary embolism.

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## **PATIENTS AND METHODS**

### **Patients:**

The present study included 59 patients who had “large-sized” or “severe” acute pulmonary embolism proven by CT. CT pulmonary angiographies were done at Radiology Department—Ain Shams University Hospital between early 2017 to late 2021. Patients were followed for their clinical outcome through 1 to 3 months after the diagnosis of acute PE, and were categorized into **two groups: (1)** Deaths or adverse clinical outcome group; this group is considered to have severe PE, bad prognosis, high risk for mortality and morbidity, and is expected to require aggressive treatments (thrombolytics, ICU therapies). **(2)** Survivors group with no adverse events. CT prognostic parameters were assessed and compared between groups to investigate the relationship between CT findings and patient outcome.

**Patients’ outcomes** were evaluated by reviewing hospital records of the included cases or by contacting patients or treating doctors. The primary study outcome was PE-related death within 30-90 days. Because of the low number of deaths, and to allow a more meaningful statistical analysis, indicators of bad prognosis or adverse outcome has been expanded to include major PE morbidity events or clinical deterioration necessitating aggressive ICU treatment escalation as the need for advanced cardiac life support, respiratory support, mechanical ventilation & intubation, hemodynamic support with inotropes or vasopressors, or the need for systemic thrombolysis, which is usually considered in serious cases by the treating physicians. This combined outcome was used by previously published PE prognostic studies and large trials like the MAPPET-3 (Management Strategies and Prognosis in Pulmonary Embolism Trial-3)<sup>(6)</sup>.

**Inclusion Criteria:**

- Patients with CT diagnosed acute pulmonary embolism who have *extensive or large emboli (at least lobar PEs)*, and who could be followed for their short-term clinical outcome (a period of 30 days to 3 months).

**Exclusion Criteria:**

- Patients with major co-morbidities that affect their outcome and not related to PE, as a result, all deaths and major adverse events in the study are more probably explained only by acute PE. Important excluded comorbidities were: cardiovascular /pulmonary, cerebro-vascular disease, renal or other systemic diseases, malignancy, and a positive history of a recent operation or major trauma.

- Patients with isolated small clots of peripheral sub-segmental pulmonary branches, as they have a low risk for major adverse outcomes.

**Ethical Considerations:**

The study was approved by the Research Ethics committee of Ain shams University Hospitals. As the study did not interfere with patients' management, informed consents were not needed.

**Image Analysis for CT prognostic parameters:**

The following CT prognostic parameters or variables (table 2, figure 5) were recorded in patients' CT angiograms, while the reviewer was unaware of the clinical outcome for each case. These predictors were selected on the basis of our review of previously published PE prognostic studies <sup>(7)</sup>.

Assessing RVD; RV diameter, RV/LV ratio

RV/LV ratio is measured by calculating the ratio between the diameters of RV and LV short axes. In the axial images, calipers are placed to measure the widest diameter from the endocardial margin of the free wall for each ventricle to the interventricular septum.

RA/LA ratio is obtained by a similar way.

Assessing RVD; IVS bowing

Septal bowing is considered present if the septum is straightened or convex toward the LV on the axial images.

Assessing RVD; IVC reflux

Reflux of contrast medium is considered present when substantial degrees of contrast appear in the intrahepatic portion of the IVC as well as the hepatic veins.

Clot localization

Pulmonary emboli are classified as central or non-central (distal/peripheral), while *central emboli* are those involving the main pulmonary trunk or the left/right pulmonary artery. Pulmonary emboli are also classified as saddle and non-saddle, while *saddle emboli* are those located at the bifurcation of the pulmonary trunk and extend into both main pulmonary arteries.

Clot burden calculation

The following PE obstruction scores were calculated as determined in **table 1**; *Millers* score, *Qanadli* score, *Mastora (total)* score, *Mastora central* score. CT PE index or Pulmonary artery obstruction index (PAOI) = the calculated percentage value corresponding to the given score.

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Table (1) Scoring systems for determining clot burden on CT pulmonary angiography.

<u>Scoring system</u>	Score calculation	Max. score
<b>Miller Score</b> adapted for CT by <b>Bankier et al., 1997</b> <sup>(B)</sup>		
(n=16)	2-point scale (0 = absent, 1 = present)	16
9 segmental PAs RT lung (3 upper, 2 middle, 4 lower lobe)	A filling defect/obstruction in any branch scores 1 point.	(9 RT lung)
7 segmental PAs LT lung (2 upper, 2 lingual, 3 lower lobe)	A proximal emboli scores a value equal to the number of segmental branches arising distally	(7 LT lung)
<b>Qanadli Score</b> <sup>(Q)</sup>		
(n=20)	An embolus in a segmental PA is scored as: 0 = no defect, 1 = partial, 2 = complete occlusion	40
10 segmental PAs in each lung 3 upper lobe 2 middle lobe or lingula 5 lower lobe	A proximal emboli scores a value equal to the number of segmental branches arising distally An isolated <i>subsegmental</i> embolus is assigned = 1.	
<b>Mastora Score</b> <sup>(M)</sup>		
(n=31)	5-point scale for the degree of obstruction /each vessel 1= < 25%, 2= 25%–49% , 3= 50%–74% , 4= 75%–99%, 5 = 100%.	155
5 mediastinal PAs (PA trunk , Rt & Lt PAs, Rt & Lt interlobar PAs) 6 lobar PAs 20 segmental PAs (3 upper, 2 middle /lingula, 5 lower lobe)	Proximal findings <b>not</b> count for distal arteries	
<b>Mastora (Central ) score</b>	(mediastinal and lobar PAs only , n= 11)	55

<sup>(B)</sup> Bankier, A. A., Janata, K., Fleischmann, D., Kreuzer, S., Mallek, R., Frossard, M., Domanovits, H., & Herold, C. J. Severity assessment of acute pulmonary embolism with spiral CT: evaluation of two modified angiographic scores and comparison with clinical data. *Journal of Thoracic Imaging*. 1997;12(2):150–158

<sup>(Q)</sup> Qanadli, S. D., El Hajjam, M., Vieillard-Baron, A., Joseph, T., Mesurolle, B., Oliva, V. L., Barré, O., Bruckert, F., Dubourg, O., & Lacombe, P. New CT Index to Quantify Arterial Obstruction in Pulmonary Embolism. *American Journal of Roentgenology*. 2001;176(6):1415–1420.

<sup>(M)</sup> Mastora, I., Martine, R., Masson, P., & Remy, J. Severity of acute pulmonary embolism : evaluation of a new spiral CT angiographic score in correlation with echocardiographic data. *Eur Radiol*. 2003;13(1):29–35.

### **Measuring vessels diameters:**

The diameter of the main PA is measured on the transverse image at the level of the PA bifurcation or the right PA where it is in contiguity with the main PA.

The diameter of the SVC is measured on the axial CT image at the location where the azygos vein joins the SVC. The diameter of the azygos vein is measured at the location where it joined the SVC.

The pulmonary infarct and pleural effusion are identified on CTPA chest images.

### **Statistical Analysis:**

Statistical analysis serves as the foundation for our study. This was achieved by using SPSS software (Statistical Package for the Social Sciences version 25 IBM Inc., USA.).

**Input variables of the study** (i.e. CT prognostic predictors, table 2) were expressed as mean values with standard deviation or

median with range for continuous variables (such as age, CT numerical measurements like RV/LV ratios or clot burden scores; normally distributed or not), and as numbers and frequencies for categorical variables (such as gender, presence or absence of IVS bowing or IVC reflux). Continuous variables could be dichotomized into categories above & below a selected cut-off (for example, RV/LV ratio < and ≥1).

**Outcome of the study** is binary i.e., coded as 0 and 1 in SSPS, where 1=death/adverse events and 0=no adverse events. To assess significant relation between CT parameters & patient outcome, appropriate

**statistical tests** (using 4 main approaches) were done, with a probability value less than 0.05 (P < 0.05) tells a statistically significant test;

- (1) **Comparisons** of frequencies or means of CT parameters between study outcome groups using Chi-square ( $\chi^2$ ) test (crosstabs) or Fisher exact test (If n < 5) for categorical variables, and Student t-test or Mann Whitney U test for continuous variables with parametric or non-parametric (non-normally distributed) data, respectively (table 2).
- (2) **Correlations** between study variables using Spearman's rho and Pearson's

tests (r) according to distribution of variables (table 2).

- (3) Each individual CT parameter was submitted to univariate binary **logistic regression** to predict odds ratio (OR) (Exp (B) in SSPS) for the dichotomous/binary outcome with 95% confidence intervals (CI) (table 4). Significant variables (p <0.05) in univariate analysis were included further in multivariate logistic regression model (table 4) to find the most independent predictors for adverse outcome, after adjusting/excluding confounders.
- (4) For predictors that manifested significant associations with patient outcome, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated (table 5). Receiver operating characteristic (ROC) curves analysis was performed where each sensitivity is plotted against the value of one minus specificity (1 – specificity) resulting in a curve; optimal cut-off values were identified for continuous variables to detect adverse outcome, for which sensitivity equaled specificity for measurements ; areas under the curve (AUCs) were calculated to determine the efficacy of each variable, and analyze the best prognostic CT parameter for acute PE patients (table 3, figure 3).

**Table (2) Prognostic CTPA signs in our study**, and results of comparison of means / frequencies between outcome groups.

CT Parameters	Comparison of means/frequencies between outcome groups				Correlation with outcome		
	Adverse outcome (28 case)		Good outcome (31 case)		P value (sig)	r	p
	Mean/No.	±SD %	Mean/No.	±SD %			
Age, years	57.8	±14.3	47.9	±13.0	.008	.301	.020
Sex, male	8	28.6%	10	32.3%	.759	-.040	.764
LV diameter , mm	34.4	±7.0	36.0	±4.7	.307	-.192	.146
RV diameter, mm	49.1	±4.0	40.6	±7.0	.000	.574	.000
RV/LV ratio	1.48	±.29	1.16	±.33	.000	.468	.000
LA diameter, mm	36.6	±7.7	35.6	±5.9	.556	.079	.553
RA diameter, mm	57.2	±8.6	46.5	±7.8	.000	.540	.000
RA/LA ratio	1.61	±.37	1.34	±.34	.003	.388	.002

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Millers score	13.6	±3.6	11.8	±4.2	.103	.214	.103
Qanadli score	25.3	±9.6	18.0	±8.2	.002	.399	.002
Mastora (central)	30.4	±13.2	19.0	±10.1	.001	.426	.001
Mastora score	78.1	±29.3	43.0	±19.5	.000	.601	.000
PA diameter, mm	32.1	±4.3	28.4	±3.5	.001	.429	.001
SVC diameter, mm	20.4	±2.4	18.0	±3.9	.016	.316	.015
Azygos diameter, mm	8.2	±1.8	7.7	±1.6	.330	.088	.509
IV septum abnormal	16	27.1%	8	25.8%	.014	.319	.014
Reflux IVC	19	67.9%	10	32.3%	.006	.356	.006
Reflux Azygos	11	39.3%	7	22.6%	.164	.181	.170
Parenchymal changes	9	32.1%	16	51.6%	.131	-.197	.135
Pleural effusion	3	10.7%	6	19.4%	.357	-.120	.365
Central PE	25	89.3%	20	64.5%	.026	.291	.025
Saddle PE	8	28.6%	8	25.8%	.811	.031	.815

Table (3) Results of ROC analysis of study predictors of PE outcome (continuous variables).

CT Parameters	ROC, for continuous variables /OUTCOME				
	AUC	CI 95%		p	Cut off
Age, years	.674	.537	.810	.022	52.5
RV, mm	<b>.831</b>	.722	.940	.000	<b>44.5</b>
RV/LV	<b>.771</b>	.650	.892	.000	<b>1.23</b>
Qanadli	<b>.728</b>	.595	.860	.003	<b>20.5</b>
Mastora(C)	<b>.746</b>	.618	.874	.001	<b>23</b>
Mastora	<b>.847</b>	.747	.948	.000	<b>62.0</b>
PA, mm	<b>.747</b>	.620	.873	.001	<b>29.5</b>
SVC, mm	.681	.546	.816	.017	19.5

**RESULTS:**

The final study included 59 patients, separated into two groups according to their clinical outcome within 1-3 months period of follow-up; 28 (47%) patients had adverse clinical events related to acute PE, and 31 (53%) patients with non-adverse (good) outcome. Adverse events in our study included: 5 deaths (8.5% mortality rate), 19 (32.2%) aggressive ICU treatments, and 20 (33.9%) patients received thrombolytic therapy. Mean age was significantly higher in the adverse than in the non-adverse outcome group (p 0.008, OR 1.057, AUC 0.674, cutoff 52.5 yrs.). No significant difference was found in sex distribution between study groups (table 2).

**RV/LV ratio & RV diameter:**

In our study population, the mean RV/LV ratio was 1.31±0.35 (range, 0.74-1.96), and the mean diameter of the RV was 44.6 ±7.1 mm (range, 27-58 mm). A highly significant difference was observed between adverse and non-adverse outcome patients for both parameters (p= .000); RV/LV ratio (1.48± 0.29 vs 1.16±0.33) and RV diameter (49.1±4.0 mm vs 40.6±7.0 mm) (table 2). Results of the univariate logistic regression analysis showed statistically significant relationship between both RV/LV ratio and RV diameter, and PE-related adverse outcome, with odds ratios OR 17.86 (95% CI: 3.16-100.7, p.000) for RV/LV ratio, and OR 1.28 (95% CI: 1.12-1.45, p .001) for RV diameter (table 4).

ROC curve analysis to predict PE adverse outcome revealed an area under the curve (AUC) of 0.771 (95% CI 0.879–0.998) for RV/LV ratio, and 0.831 (95% CI 0.650–0.892) for RV diameter (table 3, figure 3). From ROC, the optimum RV/LV ratio cutoff value for prediction of PE adverse outcome in our study lies between 1.2 and 1.4 (ideally 1.23), with a sensitivity range of 75-67.9%, & specificity of 67.7-71.0 % respectively. The optimum cutoff value for RV diameter was 44.5 mm with a sensitivity of 96.4%, & specificity 71.0% (table 5, figure 1 & 2).

**RV diameter** was shown to perform better in predicting PE adverse outcome; with a positive predictive value of 75%, positive likelihood ratio of 3.324, the highest negative predictive value of 95.7%, and a negative likelihood ratio very close to 0 (0.0507) using cutoff value  $\geq 44.5$  mm (table 5, figure 4) [comparable to PPV 67.7%, +LR 2.321, NPV 75 %, -LR 0.3692 by using RV/LV ratio at cut off  $\geq 1.23$ ] (table 5). Both were the strongest among all CT predictors, with only Mastora score having similar strong prognostic significance (table 5).

Similar to RV and RV/LV ratio, significant statistical results were shown for the RA diameter and RA/LA ratio and patient outcome (table 2). These results indicate the same underlying pathophysiology of right heart chambers overload.

No significant difference was noted in LV diameters between study outcome groups ( $p= 0.307$ ) (table 2). These results suggest that the change in RV/LV diameter ratios between study groups originated mainly from the increase in the RV diameter (RV dilatation) rather than a decrease in the LV diameter (LV under-filling) in spite of being a critical part of the pathophysiology of PE.

#### **PA obstruction scores:**

All PA obstruction scores, except Millers score, showed statistically significant relationship with PE-related adverse outcome. Mean values for Qanadli score were

significantly higher in adverse outcome patients ( $25.3\pm 9.6$ ) vs. ( $18.0\pm 8.2$ ) in the non-adverse outcome,  $p 0.002$ , with OR 1.09 (95% CI 1.027-1.16), while Mastora score:  $78.1\pm 29.3$  vs.  $43.0\pm 19.5$ ,  $p 0.000$ , OR 1.06 (95% CI 1.028-1.09), and Mastora Central score:  $30.4\pm 13.2$  vs.  $19.0\pm 10.1$ ,  $p 0.001$ , OR 1.08 (95% CI 1.031-1.13) (table 2 & 4).

ROC curve analysis revealed an area under the curve (AUC) for PA obstruction scores as follows; Mastora score 0.847 (95% CI 0.747–0.948), Mastora central score 0.847 (95% CI 0.618–0.874), Qanadli score 0.728 (95% CI 0.595–0.860). From ROC, the optimum cut off values for prediction of PE adverse outcome were 62.0 for Mastora score (sensitivity 71%, specificity 87%), and 20.5 for Qanadli score (sensitivity 57%, specificity 84%) (table 3 & 5).

Mastora score was the best discriminator score in predicting PE prognosis, with a positive predictive value of 83% , positive likelihood ratio of 5.5348, negative predictive value of 77%, and a negative likelihood ratio of 0.3283 at a cutoff value of 62.0 (table 5).

#### **PA thrombus location:**

Among the total 59 cases of our study, 45 (76%) had central PE (defined as in a main pulmonary artery), and 14 (24%) had non-central PE (lobar or peripheral only). Saddle emboli were observed in 16 (27%) (table 2). Patients with central PE had higher adverse outcomes, compared to those without central PE (55.6% vs. 21.4%;  $P=0.026$ ) with an odds ratio of 4.58 (confidence interval 95% 1.12-18.68). The rate of adverse outcome was similar for saddle and non-saddle PE groups during the follow-up period (50 % vs. 46.5%;  $P=0.811$ ) (table 2).

#### **Other CT parameters:**

Comparison of RVD qualitative findings between study outcome groups showed significant differences in leftward bowing of the interventricular septum (57.1% vs. 25.8%;  $P=0.014$ , OR 3.83; CI 95% 1.27-11.50), and contrast reflux into the IVC

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(67.9% vs. 32.3%; P=.006, OR 4.43; CI 95% 1.48-13.23) (tables 2 & 4).

The mean diameters of the pulmonary artery, and SVC, were significantly higher in adverse than in non-adverse outcome groups (P = 0.001 and 0.016) with an odds ratio of 1.33 (table 2 & 4). ROC curve revealed AUC for PA diameter = 0.747 (95% CI 0.620–0.873, p 0.001) with optimum cut off =29.5 mm (sensitivity 75%, specificity 71%) (table 3 & 5).

There was no statistically significant difference between study groups in in azygos vein diameters and other CT “qualitative” findings (i.e., pleural effusion and parenchymal lung changes) (table 2).

Table (4) Results of logistic regression of study predictors of PE outcome (univariate and multivariate analysis).

CT Parameter	<b>Binary logistic regression of study variables possibly predicting PE outcome (Univariate analysis)</b>	
	OR (95% C.I.)	P value
Age, yrs.	1.057 (1.012-1.103)	.013
RV, mm	1.28 (1.12-1.45)	.000
RV/LV	17.86(3.16-100.7)	.001
Qanadli	1.09(1.027-1.16)	.006
Mastora(C)	1.08(1.031-1.13)	.002
Mastora	1.06(1.028-1.09)	.000
PA, mm	1.33(1.103-1.61)	.003
Septum (abn)	3.83(1.27-11.50)	.017
Reflux IVC	4.43(1.48-13.23)	.008

**Final prognostic model:**

In multivariate analysis, three variables remained as significant independent predictors of PE adverse outcome (table 4): RV diameter [OR 1.318 (95% CI: 1.085-1.601, p = .005)], Mastora score [OR 1.073 (95% CI: 1.022-1.126, p = .005)], and Age [OR 1.089 (95% CI: 1.016-1.167, p = .016)]. In the final model of logistic regression combining these three parameters, 84.7% of overall cases were correctly identified (table 4). RV/LV ratio, other PE scores, and other markers such as septal bowing, IVC reflux, and vessels diameters disappeared from the model by losing significance (table 4).

CT Parameter	<b>Binary logistic regression of independent predictors of PE outcome (Multivariate analysis)</b>	
	OR (95% C.I.)	P value
Age, yrs.	<b>1.089</b> (1.016-1.167)	<b>.016</b>
RV, mm	<b>1.318</b> (1.085-1.601)	<b>.005</b>
Mastora	<b>1.073</b> (1.022-1.126)	<b>.005</b>

**Final Model (age +RV diameter + Mastora score)**  
 83.9% of correctly defined adverse outcome cases  
 84.7% of overall correctly defined cases  
 Compared to  
 74.6% RV alone model  
 78.0% MASTORA alone model  
 69.5% RV/LV alone model



Table (5) Results of accuracy indicators of study predictors of PE outcome.

CT Parameters	Sig. P-value	Accuracy of test				Likelihood ratio	
		SENS	SPS	PPV	NPV	+LR	-LR
Age $\geq$ 52.5 years	.150	60.7%	58.1%	56.7%	62.1%	1.448	0.6764
RV $\geq$ 44.5mm	.000	96.4%	71.0%	75.0%	95.7%	3.324	0.0507
RV/LV $\geq$ 1.23	.001	75.0%	67.7%	67.7%	75.0%	2.321	0.3692
RV/LV $\geq$ 1.2	.002	75.0%	64.5%	65.6%	74.1%	2.112	0.3875
RV/LV $\geq$ 1.3	.003	67.9%	71.0%	67.9%	71.0%	2.341	0.4521
RV/LV $\geq$ 1.4	.003	67.9%	71.0%	67.9%	71.0%	2.341	0.4521
Qanadli $\geq$ 18.5	.017	78.6%	51.6%	59.5%	72.7%	1.6239	0.4147
Qanadli $\geq$ 20.5	.001	57.1%	83.9%	76.2%	68.4%	3.5465	0.5113
Mastora(C) $\geq$ 23	.000	71.4%	74.2%	71.4%	74.2%	2.7674	0.3854
Mastora $\geq$ 53.5	.000	75.0%	77.4%	75.0%	77.4%	3.3185	0.3229
Mastora $\geq$ 62.0	.000	71.4%	87.1%	83.3%	77.1%	5.5348	0.3283
PA $\geq$ 29.5mm	.000	75.0%	71.0%	70.0%	75.9%	2.5862	0.3521
Septum (abn)	.014	57.1%	74.2%	66.7%	65.7%	2.2131	0.5781
Reflux IVC	.006	67.9%	67.7%	65.5%	70.0%	2.1021	0.4741
Central PE	.026	89.3%	35.5%	55.6%	78.6%	1.3844	0.3014

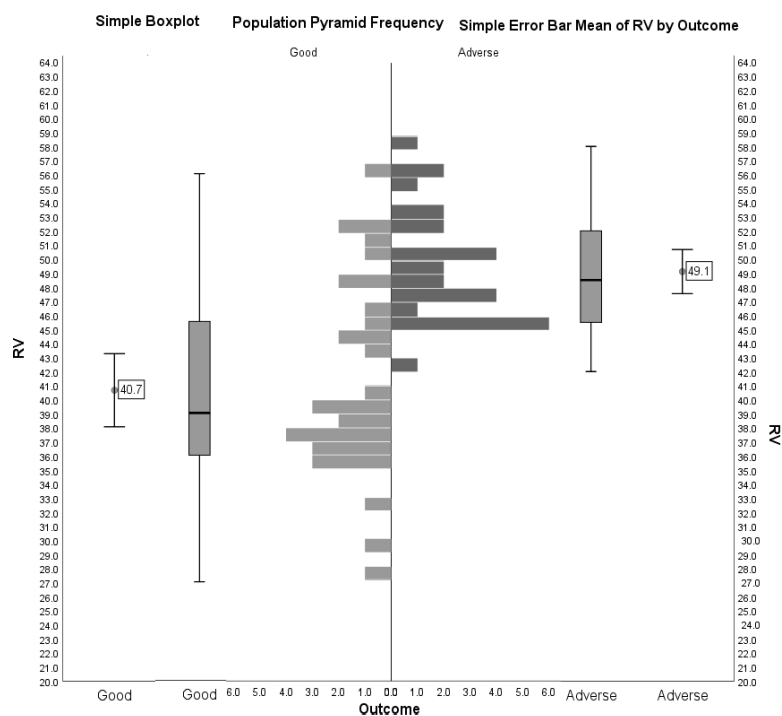


Figure (1) Histogram, box plot, and error bar of “RV diameters” (distributions and means) according to study outcome.

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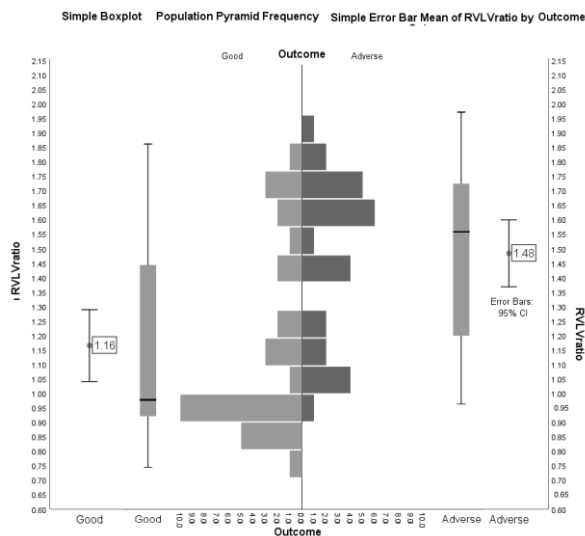


Figure (2) Histogram, box plot, and error bar of “RV/LV ratio” (distributions and means) according to study outcome.

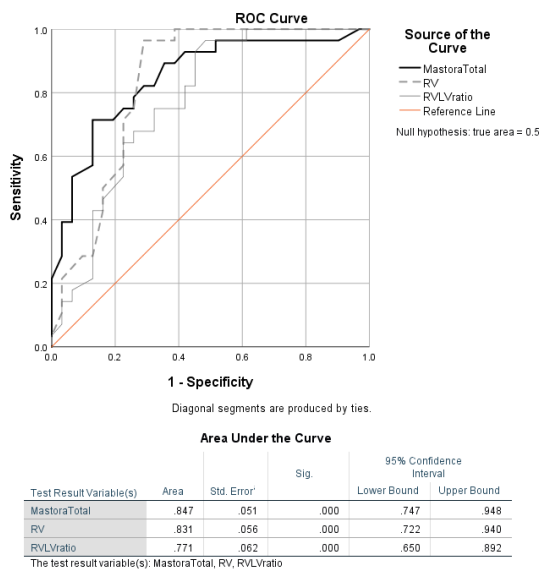


Figure (3) Analysis of ROC curve comparing RV, RV/LV ratio, and Mastora clot score to predict PE adverse outcome. Area under the curve (AUC) and optimum cutoffs values were obtained [See table 3].

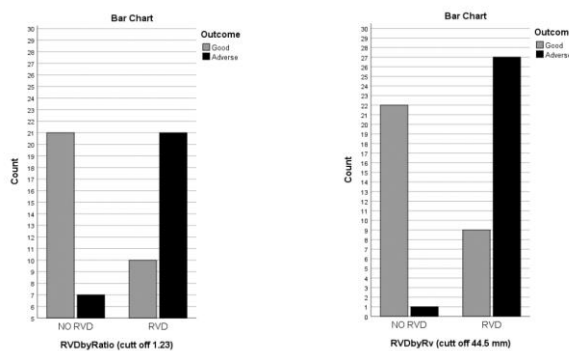


Figure (4) Frequency of PE adverse outcome according to different cutoffs of RV, RV/LV ratio. These graphs illustrate that the higher sensitivity (*the correctly defined cases with adverse*

outcome) & specificity (the correctly defined cases without adverse outcome) was obtained by using  $RV \geq 44.5$  mm cutoff. [See table 5].

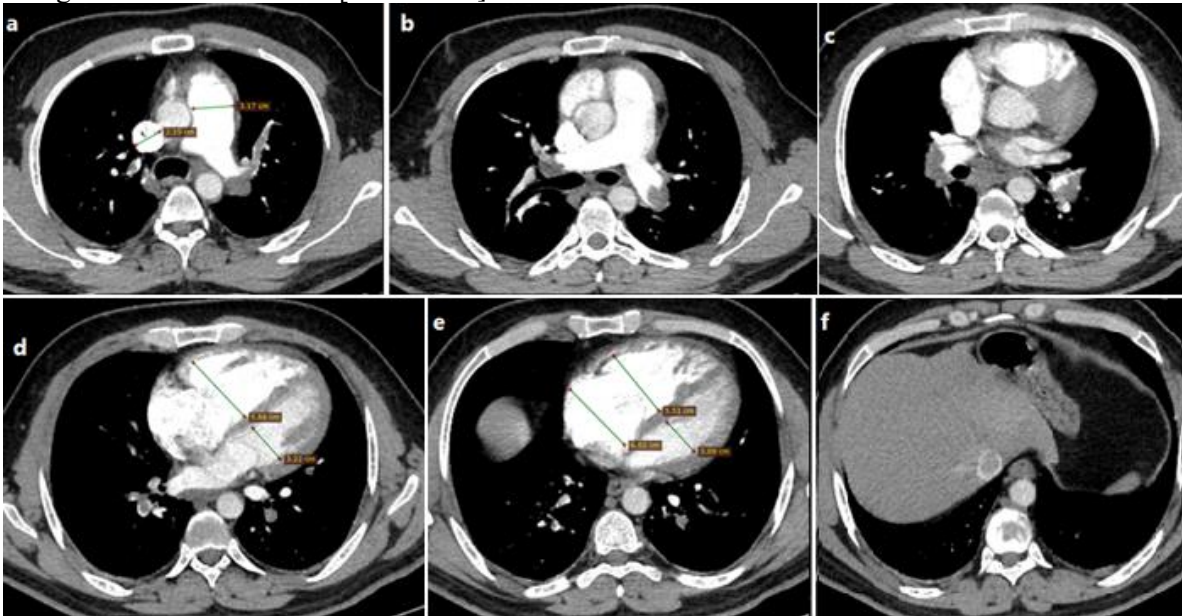


Figure (5) Case 1 an 80-year-old male patient who developed an attack of acute dyspnea & hypotension. Central PE is seen involving both main pulmonary arteries, with calculated clot load scores according to Qanadli and Mastora were 40, and 92, respectively. CTPA showed signs of RVD; RV/LV ratio=1.7, IVS bowing, IVC contrast reflux. PA diameter = 33 mm SVC 22 mm. Thrombolytic therapy was indicated, and the patient survived.

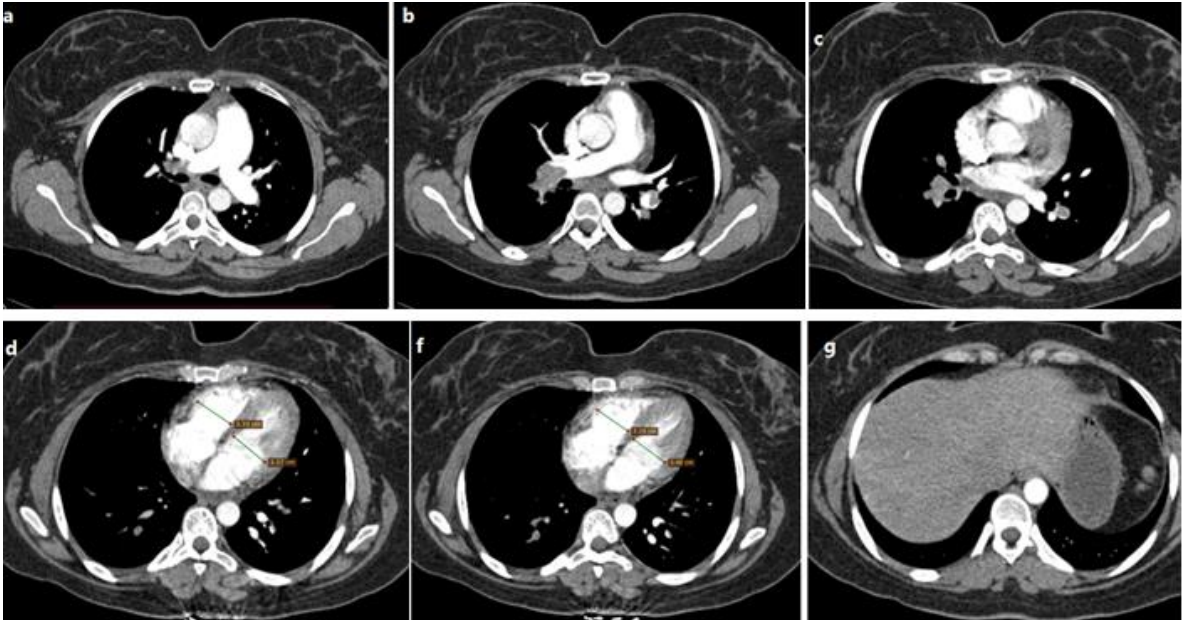


Figure (6) Case 2 a 46-year-old female patient presented with acute dyspnea. Central PE is seen involving the distal portion of the right main pulmonary artery and the left lower lobar artery. Calculated clot load scores according to Qanadli and Mastora were 25 and 54, respectively. CTPA showed no signs of RVD; RV/LV ratio=1.1, normal IVS, no IVC contrast reflux. PA diameter = 30 mm SVC = 17 mm. Thrombolytic therapy was not needed, and the patient did well.

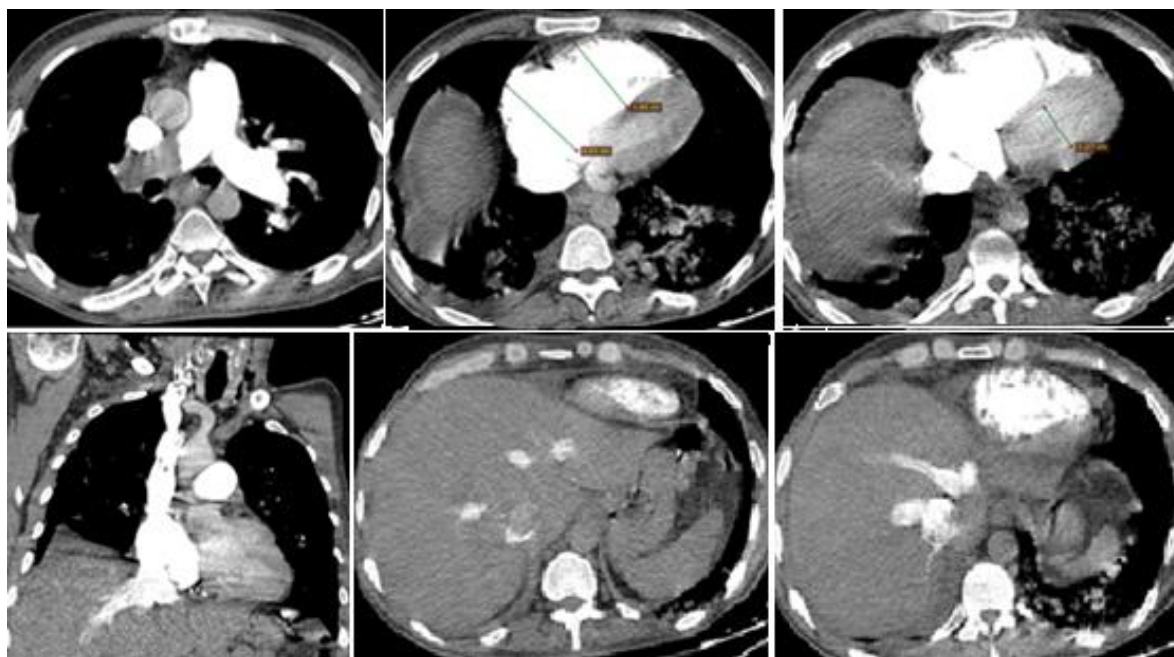


Figure (7) Case 3 a 47-year-old male patient presented with rapidly worsening dyspnea and shock. CTPA showed all typical severity markers; large obstructive central clot obstructing the right main pulmonary artery and left lobar branches, high clot burden scores (Qanadli = 30, Mastora = 131), severe RVD signs; markedly dilated RV=55 mm, increased RV/LV ratio = 1.9, ventricular septal bowing, marked contrast reflux into the IVC and hepatic veins, and left lower lobe pulmonary infarcts. The patient died 1 day after admission.

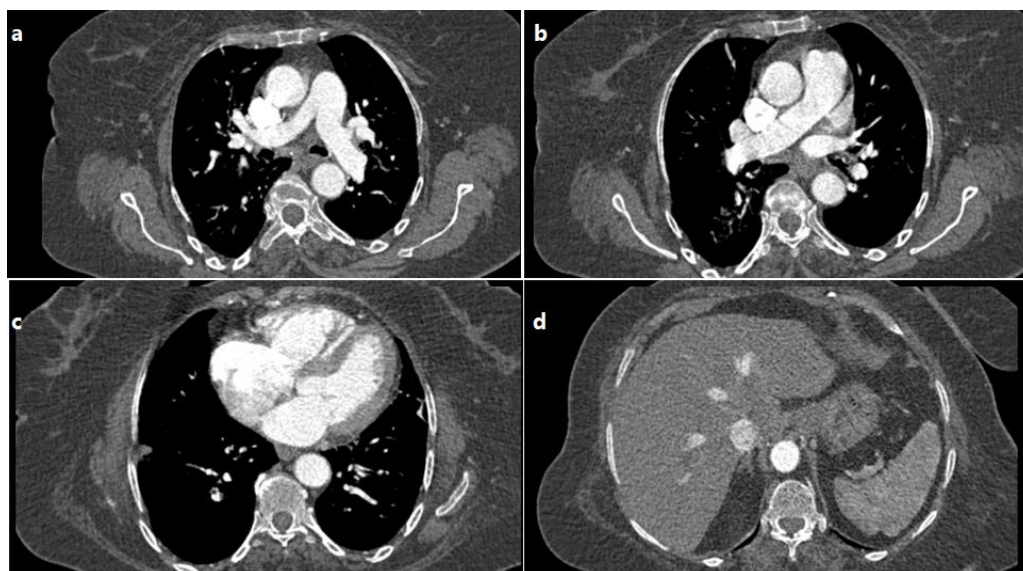


Figure (8) CTPA of a 73-year-old female patient. CTPA was negative for PE, however, contrast reflux into the IVC was obvious (d). This case confirms that contrast reflux into the IVC is not a specific sign of RVD with acute PE or PE severity. It could be seen due to technical issues such as high injection rate or patient holding breath during injection, or it may be indicative of the patient's underlying cardiac or pulmonary disease.

### Illustrative cases:

**Case 1 (figure 5)**, an 80-year-old male patient developed an attack of acute dyspnea & hypotension for 1-2 hours. Echocardiography was requested initially and revealed severe tricuspid regurgitation and dilated RV. CTPA was done and “submassive PE” was reported involving the distal portions of both main pulmonary arteries. Although the patient became stable, clinicians were worried about developing critical adverse events in view of echocardiographic & CT findings. The patient was admitted to the ICU & administration of systemic thrombolytic agent was decided after the exclusion of contraindications. The patient showed significant clinical & echocardiographic improvement & was discharged on anticoagulant therapy. In this case, in addition to the visualized central large thrombus, CTPA showed signs of RVD (RV/LV ratio=1.7, IVS bowing, IVC contrast reflux).

**Case 2 (figure 6)**, another 46-year-old female patient with central thrombus, however, didn't show signs of RVD. The patient had a good outcome and did not require thrombolytic therapies. From both cases 1 & 2, it was clear that signs of RVD were a critical determinant of the clinician's decision regarding the thrombolytic treatment & optimal management.

**Case 3 (figure 7)**, a 47-year-old male patient presented with rapidly worsening dyspnea and shock. Massive PE was diagnosed and as the patient was desaturated, he was admitted rapidly to the ICU and mechanically ventilated. Although thrombolytics were started, the patient died 1 day after admission. This case had the worst PE outcome and CTPA showed all typical severity markers; large obstructive central clot, high clot burden score (Qanadli= 30, Mastora = 131), severe RVD signs; increased RV/LV ratio = 1.9, ventricular septal bowing, marked contrast reflux into the IVC and hepatic veins. Many similar severe cases may die before doing CT.

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### DISCUSSION:

The prognostic role of CT pulmonary angiography in acute PE has been studied in literature with very contradictory results. Most prognostic studies have attempted to correlate CTPA features with “mortality” as a clinical endpoint. Several other studies have used different clinical and functional traits or less severe composite endpoints to serve as ‘intermediate phenotype’ for PE-related adverse outcomes. Also, studies have investigated the relationship between CT parameters and patients' risk categories (low, intermediate, and high-risk) according to ESC risk stratification for the estimated PE-related mortality<sup>(2)</sup>. In this study, we compare our results with the currently available evidence on the prognostic value of CT parameters frequently used in acute PE.

**The right-to-left ventricle dimension ratio** obtained by axial images is the most commonly used CTA-prognostic marker in acute PE<sup>(8,9)</sup>. It reflects acute RV dilatation, a critical event in the pathophysiology of PE mortality<sup>(10)</sup>. In a meta-analysis of 49 studies enrolling 13,162 patients, an increased RV/LV diameter ratio measured on axial CT images was associated with nearly a 2.5-fold risk for *all-cause* mortality and adverse outcome (pooled OR 2.5 & 2.3) and a 5-fold risk for *PE-related* mortality (OR 5.0)<sup>(11)</sup>. A CT RV/LV diameter ratio cutoff value of 0.9 or 1.0 is conventionally employed to detect RV overload, according to ROC analysis and for the best sensitivity and specificity from many studies<sup>(12)</sup>. “Normal” CT RV/LV diameter ratio was shown to have a high negative predictive value for death due to PE (NPV up to 100%), making CTA useful to identify low-risk patients<sup>(13)</sup>.

In agreement with earlier studies, **RV/LV ratio** was a significant predictor of PE outcome in our study (table 2), with an odds ratio OR of 17.86 (95% CI: 3.16-100.7, p.000) and adequate sensitivities (68-75%)



and specificities (65-71%) using different cutoffs (tables 4 & 5).

Contrarily to the wide agreement on the advantageous use of RV/LV ratio as a measure of RVD in previous studies, **RV diameter** alone performed better in predicting PE adverse outcome in our study; OR 1.28 (95% CI: 1.12-1.45, p.001) and was a significant independent predictor in multivariate analysis; OR 1.318 (95% CI: 1.085-1.601, p.005) (table 4). The resulting wide CI of odds ratio for RV/LV ratio in our study and the relatively low sensitivity and specificity (compared to RV diameter, table 5) indicate an underlying influence of LV diameter, which was not related to the outcome in our study (p.307, table 2). LV size depends on other confounding factors, such as the presence of pre-existing chronic respiratory or cardiovascular disease, which may alter the RV/LV diameter ratio even in front of RV enlargement<sup>(14,15)</sup>. RV diameter showed the highest negative predictive value for an adverse outcome (96 %) with a negative likelihood ratio very close to 0 (0.0507) (table 5).

These findings have crucial implications. CT-assessed RV enlargement in acute PE, even in low-risk patients triaged by using clinical prognostic scores (PESI class I or II or sPESI 0), was classified as impending hemodynamic instability, although patients may appear stable at presentation. The recent ESC guidelines suggest upgrading these patients from the low to the intermediate–low-risk class, making them potentially ineligible for outpatient or home management<sup>(2,16,17)</sup>. Although RVD on CT cannot yet be used as the sole tool for PE risk stratification and treatment upgrading regarding thrombolytic therapy, these data strongly support the need for routine radiological reporting of the RV/LV ratio at every CTPA exam<sup>(18)</sup>.

**The pulmonary embolic burden** can be estimated at CTA either by localization of the emboli or by counting the number of

occluded vessels and degree of obstruction (embolic burden obstruction score, table 1). The literature shows mixed results when it comes to the usability of CT-derived obstructive indices in PE mortality prediction, with the bulk of the studies did not find significant association with mortality<sup>(19,20)</sup>. Therefore, the unusual conclusion that “size does not matter” has been supported by many authors. Moreover and unexpectedly, few studies showed that a higher embolic burden may associated with a decreased risk of death! This may be due to survival or selection bias, as patients with massive PE may not survive to undergo CT imaging<sup>(21,22)</sup>. Indeed, PA clot scores suffered from methodological issues. From a pathophysiological perspective, mechanical obstruction alone (the size and distribution of thrombi) may not account for all PE adverse effects. A more important factor is how the RV responds to the increase in pulmonary vascular resistance. PA clot load scores do not consider comorbidities and cardio-pulmonary status of the patients, which can influence their outcomes. It was assumed that these fixed scores are too simplistic to account properly for the functional impact of emboli, and therefore were unable to predict morbidity in several studies<sup>(23)</sup>.

Our study results supported the use of pulmonary artery obstruction scores as an indicator of PE severity/adverse outcome. Qanadli, Mastora, and Mastora central scores were significantly higher in patients with adverse outcome (table 2). Millers score was not associated with patient outcome (p 0.103), and this can be explained by the design of the score itself (table 1). The optimal cutoff for Qanadli score was 18.5 - 20.5, and for Mastora score was 50.5 - 62, corresponding to PE index of 40%-50% reported by other studies (table 3 & 5). Mastora score was a strong multivariate predictor of adverse outcome, and showed an excellent discriminatory ability (AUC= 0.847; p 0.000) that is comparable to RV diameter performance (table 3 & 5).

Although more complicated and time-consuming, Mastora score was more hemodynamically "sensible" than the other severity indices due to the 5-point grading system used to rate each central and peripheral pulmonary artery branch (table 1).

**Central clot location** can be of value as a prognostic marker for rapid risk stratification of PE. In contrast to obstruction scores, the classification of PE according to its most proximal level is frequently included in radiology reports and easier to understand by the physician<sup>(24,25)</sup>. In agreement with multiple studies and meta-analyses<sup>(19&25)</sup>, our study demonstrated that clinical prognosis in patients with PE is significantly influenced by PE location, and large proximal pulmonary emboli are expected to have more serious consequences (table 2).

In contrast, despite the high frequency of saddle PE cases in our study (16 patients of 59 study cases), we did not observe higher rates of PE adverse events in patients with saddle PE (table 2). Based on these results, our study is consistent with conclusions drawn from other studies that "central rather than saddle" PE can predict unfavorable outcomes in acute PE patients<sup>(26)</sup>. Although saddle PE is often viewed as a worrisome sign to clinicians, the data at hand could not support aggressive treatment or thrombolytic therapy in these cases, particularly in the absence of hypotension<sup>(27)</sup>.

**Sizes of main PA, SVC, & azygos vein, displacement of the interventricular septum, & the presence of contrast reflux into inferior vena cava or azygos** have been proposed as CT markers of elevated right heart pressures in patients with acute PE. However, these markers showed a high degree of inter-observer variability and were unreliable for their potential utility in predicting adverse outcomes of PE<sup>(28)</sup>. These markers showed results with low sensitivity and specificity in our study (table 5).

**Ventricular septum bowing** is affected by the plane of detection & by septal movements through the cardiac cycle in "non-gated" CT, which explains the low sensitivity<sup>(29)</sup>. **Retrograde opacification of the IVC & hepatic veins** could be encountered many times during CTPA (figure 8). This finding may be related to a high injection rate of contrast, or right-sided heart diseases like right heart failure, tricuspid regurgitation, or pulmonary hypertension, which explains the low specificity<sup>(30)</sup>. Still, and consistent with previous reports<sup>(31,32)</sup>, we sought that extensive (sub hepatic) IVC reflux should be considered as a severity sign in PE that may immediately identify patients at risk as soon as the diagnosis is done by CTPA (figure 7).

**Measurements of veins' diameters** may range widely and are highly dependent on breathing. Therefore, we cannot recommend their use in the prognostic assessment of patients with PE<sup>(28)</sup>. On the other hand, **PA diameter** showed better discrimination between study outcome groups at a cutoff of 29.5 mm (table 3 & 5). This is comparable to the cutoff for predicting the presence of pulmonary arterial hypertension used in the literature<sup>(33-35)</sup>.

There are several limitations of our study that require emphasis. First, the study included only patients with more serious PE clots and no underlying comorbidities. This could have led to "selection bias" that may influence the prevalence of CT findings in study population. Second, categorization of patients according to their outcomes was a complex process and possibly carry degrees of "subjectivity". Third, cardiovascular measurements were done on non-ECG gated axial images only. ECG-gated CT is not commonly used in acute PE patients since it has been shown to increase radiation exposure while with only modest gains in measurement accuracy<sup>(36)</sup>. Fourth, our study focused only on the performance of CT parameters in PE prognosis, with little

comparison to echocardiography, cardiac biomarkers, or detailed patient clinical data. The inclusion of all these data limits the total number of patients that can be enrolled in this study, because it is unlikely to locate all these data available for all patients in various emergency settings. Despite these limitations, we argue that such biases do not necessarily affect the validity of the results or change the main conclusions of the study.

### **Conclusion:**

Our study supported the use of CTPA-derived indicators of right ventricular dysfunction and pulmonary artery obstruction scores as prognostic predictors in patients with acute PE. Physicians should seize the opportunity and use information already available from CTPA, even in stable PE patients, as these indicators may be sufficient to identify patients at increased risk of PE-related adverse events.

### **Conflict of interest:**

There is no conflict of interest

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## الدور التنبؤي لتصوير الأوعية الرئوية بالأشعة المقطعية في مرضى الانسداد الرئوي الحاد أيمن محمد محمد خليفة<sup>١</sup> ، فاتن محمد محمود كامل<sup>٢</sup> ، عصام محمد عبد الحافظ<sup>٢</sup> ، عمرو عامر<sup>١</sup>

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**المقدمة:** قام عدد متزايد من الدراسات في السنوات القليلة الماضية بالبحث عن دور تنبؤي محتمل للأشعة المقطعية متعددة المقاطع لتحسين تصنيف مخاطر الانسداد الرئوي ، مرفقة بتفاصيل محيرة ونتائج غير متجانسة. تم ترشيح بعض معايير التصوير بالأشعة المقطعية لهذا الغرض. كانت نسبة قطر البطين الأيمن الى البطين الأيسر ومقياس انسداد الشرايين من أكثر المعايير التي تمت دراستها على نطاق واسع.

**الهدف من البحث:** هو دراسة الدور التنبؤي لتصوير الأوعية الرئوية بالأشعة المقطعية في مرضى الانسداد الرئوي

الحاد.

**المرضى والطرق والحالات:** تمت متابعة ٥٩ مريضاً من المرضى الذين يعانون من الانسداد الرئوي الحاد "الشديد أو الكبير الحجم" تم تشخيصها عن طريق تصوير الأوعية الرئوية بالأشعة المقطعية وذلك خلال ٣٠ يوماً إلى ٣ أشهر لتقييم نتائجهم السريرية على المدى القصير. تضمنت مؤشرات النتائج السلبية: الوفيات المرتبطة بالانسداد الرئوي الحاد ، والتدهور السريري وضرورة العلاج المكثف يوحد العناية المركزة أو مذيبيات الجلطة. تم تقييم العلامات التنبؤية بالأشعة المقطعية للمرضى وتحليلها إحصائياً لتحديد قدرتهم على التنبؤ بالنتائج السلبية الرئيسية للانسداد الرئوي الحاد.

**النتائج:** من بين جميع العلامات التنبؤية بالأشعة المقطعية ، كان قطر البطين الأيمن هو أفضل مميز بين مجموعتي النتائج السلبية وغير السلبية في دراستنا ، ويمكن مقارنته فقط بمقياس ماستورا لدرجة انسداد الشريان الرئوي ، وقد أظهر أعلى قيمة تنبؤية سلبية ٩٥,٧٪ ونسبة احتمال سلبية قريبة جداً من ٠. كان أداء قطر البطين الأيمن وحده أفضل من نسبة قطر البطين الأيمن الى البطين الأيسر الشائعة الاستخدام كمقياس لتمدد البطين الأيمن في التنبؤ بنتائج سلبية للانسداد الرئوي. انحناء الحاجز، الدرجات الكبيرة من ارتداد مادة التباين الى الوريد الأجويف السفلى ، وأقطار الشريان الرئوي و الوريد الأجويف العلوي أظهرت حساسية ونتائج نوعية ضعيفة. كان نموذج الانحدار اللوجستي النهائي الذي يجمع بين ثلاث علامات (قطر البطين الأيمن + مقياس ماستورا + العمر) قادراً على تحديد ٨٣,٩٪ من حالات النتائج السلبية و ٨٤,٧٪ من الحالات الإجمالية في دراستنا بشكل صحيح.

**الخاتمة:** دعمت دراستنا استخدام العلامات المشتقة من الأشعة المقطعية لضعف البطين الأيمن و مؤشرات درجة انسداد الشريان الرئوي كعلامات تنبؤية في المرضى الذين يعانون من الانسداد الرئوي الحاد.