Central Clot Score at Computed Tomography as a Predictor of 30-day Mortality after Acute Pulmonary Embolism

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Abstract

Introduction: The severity of acute pulmonary embolism can be assessed with computed tomography (CT) using clot burden estimation. We compared the existing CT obstruction scores with an in-house developed central clot score for the prediction of 30-day pulmonary embolism (PE)-related mortality. Materials and Methods: In 125 consecutive patients [47 men, 78 women; mean age \pm standard deviation (SD, 60.4 years \pm 16.6] with acute PE, 2 readers in consensus assessed the severity of PE with 2 existing clot scoring systems (Mastora and Qanadli) and central clot score. The right ventricular dysfunction was assessed by right ventricular diameter (RVD), left ventricular diameter (LVD), ventricular ratio (VR) and septal deviation. Univariate and multivariate regression analysis were performed to correlate these parameters and 30-day PE-related mortality. Results: Ten patients (8%) died of PE within 30 days following CT and 115 patients did not have PE-related death outcome. There was a significant difference in all 3 clot scores, LVD and VR between patients with 30-day PE-related death and those without ($P \leq 0.001$ -0.02). Univariate regression analysis showed that all three clot scores and LVD were predictors of PE death, however with multivariate analysis, only central clot score showed significant correlation with 30-day PE death [Odds ratio (OR), 1.1; 96% CI, 1-1.16; P <0.003]. A central clot index of 53% had 100% sensitivity, 76.5% specificity, 23.5% positive predictive value and 98% negative predictive value for 30-day PE death. Conclusion: Central clot score is a strong predictor of 30-day PE death and may therefore allow therapy and risk stratification in patients with acute PE.

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Key words: Clot burden, Pulmonary embolism, Severity, Short-term outcome, Thromboembolism

Introduction

Multi-detector Computed Tomography (MDCT) pulmonary angiography is currently the method of choice for the detection of acute pulmonary embolism (PE), because of its convenience, speed, sensitivity, direct clot visualisation and ability to provide alternative diagnoses that mimic PE clinically.¹⁻⁵

Defining CT severity criteria may help to stratify the risk of patients, indicate prognosis, guide treatment selection, and provide an accurate method to monitor the efficacy of treatment.^{1,6} Many investigators have recently shown that the severity of PE can be estimated with scoring systems.⁶⁻¹⁷ Typically, obstruction index of more than 40% to 60% correlates with severe PE. Some studies have also suggested that right heart strain and embolic burden at CT are prognostic findings.^{11,12,14,16,17} However, the utility of CT in the stratification of patient treatment and prediction of short-term outcome is still under investigation.6,11,18

Previous scoring systems based on obstruction of crosssectional area of the pulmonary arterial circulation ^{6,8,13} are relatively time consuming and not easily applicable in practice. A simpler and faster scoring system is therefore desirable. Since the central pulmonary arteries have the lowest cross-sectional area compared to the summed crosssectional areas of the peripheral pulmonary arteries, ¹⁹ emboli in the central arteries may have the greatest impact on these scores. Right ventricular dysfunction is also found in a higher proportion of patients with central PE (mediastinal and lobar arteries) as compared to those with peripheral PE (segmental and sub-segmental arteries).¹⁹ It therefore seems reasonable that an obstruction score applied only to the central arteries may be useful for the prediction of the clinical outcome of PE.

We therefore evaluated a central score system including

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only the central pulmonary arteries known as central clot score. The objective of our study was to compare the central clot score system with the existing scoring systems^{6,13} for the prediction of 30-day PE-related mortality.

Materials and Methods

Patients

Institutional research review board approval was obtained for the retrospective study and no informed consent was needed. This observational study involved a consecutive cohort of 716 patients who underwent CT pulmonary angiography (CTPA) at our institution for clinical suspicion of acute PE between May 2001and December 2004. PE was diagnosed in 131 patients (18.3%). Four patients with no treatment/follow-up data and 2 patients with no CTPAs available for review were excluded from the analysis. The final study group consisted of 125 patients. Thirty-day PE-related mortality was the primary outcome assessed. Mortality, demographics, causes of death were entered in the hospital discharge summary, comorbidities (congestive cardiac failure, neoplasm and chronic lung disease) and recent events leading to PE (trauma, surgery and immobilisation) were assessed using a hospital electronic database. All patients were followed-up for 30 days or more.

CT Pulmonary Angiography (CTPA)

CTPA was performed on a MDCT scanner (Volume Zoom, Siemens, Forchheim, Germany).

The parameters were: 4 x 1 mm collimation; 6 mm/sec table speed; 120 to 140 kV and 140 to 180 mA. Scans were performed in the caudo-cranial direction from below the domes of the diaphragm to the apices of the lungs at maximal inspiration in one breath hold. A total of 100 to 130 mL of non-ionic contrast medium was injected at a rate of 3 to 4.5 mL/sec through an 18 or 20G intravenous cannula placed in a peripheral vein, using an automated injector device (Envision CT; Medrad, Pittsburg, PA). The scan delay was determined by a bolus tracking software with a small region of interest placed over the main pulmonary artery. Scanning was initiated 4 seconds after the contrast enhancement of the main pulmonary artery reached 100 Hounsfield Units. The mean duration of data acquisition was 14 seconds (range, 10 to 16). The raw image data comprising 1 mm thick transaxial scans were archived. Axial images that were 3 mm were sent for routine reporting.

Image Analysis

The CTPAs were read in consensus by 2 experienced readers (SKV, WSC) with 10 and 17 years of experience in chest CT. Emboli were identified in pulmonary arteries until the sub-segmental artery level on axial 1 mm images and scored according to the scoring systems. Visual analysis of a vessel was performed on the image showing the vessel best. Readers were blinded to clinical data and outcome of patients. For each patient, the main pulmonary artery, right and left pulmonary arteries, descending pulmonary arteries, 3 lobar (upper, middle/lingula and lower) arteries, 20 segmental arteries and 40 sub-segmental arteries were assessed. A total of 71 arteries in each patient were evaluated on MDCT and scored. CT measurements of right ventricular dysfunction, namely maximum internal diameters of right ventricle (RVD) and left ventricle (LVD), ventricular ratio (VR = RVD/LVD) and septal deviation (interventricular septum is rectilinear or convex to the left) were also determined.

Pulmonary Artery Obstruction Indices

Three pulmonary artery obstruction indices were calculated for each patient. The scoring systems compared are summarised in Table 1.

The first score was according to the scoring system described by Qanadli et al.⁶ In this system, each lung is regarded as having 10 segmental pulmonary arteries. The index is defined as the number of segmental artery branches that are blocked with emboli and multiplied by a factor of 1 for partial blockage or a factor of 2 for a completely obstructive PE. Emboli in the sub-segmental artery findings were assigned a value of 1. With this scoring system, the highest possible score is 40 which corresponds to a 100% obstruction index.

The second score was obtained with the system described by Mastora et al.¹³ The scoring system includes 5 mediastinal (main pulmonary artery, right and left pulmonary arteries, right and left interlobar pulmonary arteries), 6 lobar pulmonary arteries, and 20 segmental arteries (3 in upper lobes, 2 in middle lobe or lingual, and 5 in the lower lobes on each side). The severity score is based on the percentage of luminal obstruction in the arteries by emboli and each artery scored for the degree of luminal obliteration on a scale from 0 to 5 (0 = 0%, 1 = 1% to 24%, 2 = 25% to 49%, 3 = 50% to 74%, 4 = 75% to 99%, 5 = 100%). The sum of mediastinal, lobar and segmental arteries scores gives a global score with a maximum of 155 which corresponds to a 100% obstruction index.

For the third scoring system, central clot score, we only scored 11 central pulmonary arteries (5 mediastinal and 6 lobar arteries). The proximal artery was given a score equal to the number of segmental arteries arising distal and the degree of occlusion was graded 0 to 5 (0 = 0%, 1 = 1% to 24%, 2 = 25% to 49%, 3 = 50% to 74%, 4 = 75% to 99%, 5 = 100%). The maximum possible score is 55 which corresponds to a 100% obstruction index. For statistical analysis, the scores were converted to a percentage index [(observed score/maximum score) x100] and compared.

Scoring system	Arteries scored	Weighting	Maximum score
Qanadli et al ⁶	10 segmental arteries for each lung (total 20)	0 = normal 1 = partial 2 = total	40
Mastora et al ¹³	5 mediastinal, 6 lobar and 20 segmental arteries (total 31)	0 = 0% $1 = 1-24%$ $2 = 25-49%$ $3 = 50-74%$ $4 = 75-99%$ $5 = 100%$	155
Central Score	5 mediastinal and 6 lobar (total 11)	0 = 0% $1 = 1-24%$ $2 = 25-49%$ $3 = 50-74%$ $4 = 75-99%$ $5 = 100%$	55

Table 1. Pulmonary Clot Scoring Systems*

* Within each system, the relevant artery is scored according to the degree of obstruction and the total number of weighted scores is then summed to obtain the overall score.

Statistical Analysis

Statistical analysis was performed with commercially available software (SAS version 6, Cary, NC US). Continuous variables were expressed as mean ± standard deviation or range when appropriate. The distribution of age, sex, comorbidities, recent events, treatment received and CT characteristics between patients who suffered PErelated death and those who did not were compared using the Fisher's exact test for binary variables and Student's t-test for continuous variables. Correlation between clot scores and CT measurements of right ventricular dysfunction were determined using Pearson's coefficient. The correlation between clot scores, CT measurements of right ventricular dysfunction and occurrence of 30-day PE-related death was determined using univariate logistic regression. Multivariate backward stepwise logistic regression was performed on significant univariate factors. This procedure selects the best predictors until all remaining variables of the tested model are significant. Odds ratios were calculated with 95% confidence interval. In all outcome analyses, multivariate stepwise and univariate logistic regression were corrected for age and sex. Statistical significance was set at 5% (*P* < 0.05).

Results

Patients

The study population consisted of 78 females and 47 males with mean age 60.4 years (range, 16 to 94). The mean follow-up period was 233.2 days (range, 1 to 1065). There were 115 inpatients (92%), 2 outpatients (1.6%) and 8 patients who had emergency admissions. Thirty patients had cardiopulmonary disease and 21 patients had a medical history of previous thromboembolism. Thirty-seven patients

(29%) had a medical history of neoplasm and 36 patients had recent surgery (Table 2). Among the inpatients, 21 patients (16.8%) were in intensive care unit when PE was diagnosed. There were no significant differences in the incidence of co-morbidities and recent events leading to acute PE in the two outcome groups. All patients who survived beyond the 30-day outcome assessment period had a mean follow-up of 253 (\pm 222 days SD) days as compared to 5.3 days (\pm 7.6 days SD) for patients with PE death (P < 0.001).

Treatment

Treatment for acute PE was given to 115 patients. Anticoagulation therapy (heparin followed by warfarin) was given to 93 patients (74.4%), 6 patients (4.8%) received inferior vena cava (IVC) filter only, 4 patients (3.2%) received anti-coagulation therapy with IVC filter insertion, 10 patients (8%) received intravenous thrombolysis and 2 patients (1.6%) underwent surgical embolectomy. Ten patients (8%) did not receive any treatment due to comorbidities (n = 6) or terminal illness (n = 4) (Table 2). ICU patients received more aggressive treatment, that is, thrombolysis and embolectomy as compared to the non-ICU patients (33.3% vs 4.8%). Age, sex, history of cardiopulmonary disease or venous thromboembolism did not influence the treatment received by the patients.

Clot Score

The mean clot index in the study population was 24.8%, 33.5% and 33% for the Mastora, Qanadli and central clot scores, respectively. The Pearson correlation for comparisons between clot scores from each scoring system ranged from 0.85 to 0.89 (P < 0.001), which indicated significant correlation. Univariate and stepwise backward logistic regression analysis showed that there was no

Characteristic	PE-related Death in 30 Days (n = 10)	No PE-related Death in 30 days (n = 115)	P value*	
Demographics				
Mean age (y)†	59 ± 17.6	60.6 ± 16.6	0.78	
Female/Male	8/2	70/45	0.20	
Comorbidities				
Neoplasm	3	34	0.41	
Congestive cardiac failure	3	27	0.55	
Chronic lung disease	0	6	0.60	
Recent events <30 days prior to PE				
Major surgery	2	34	0.41	
Trauma	0	3	0.77	
Treatment received for PE				
Anticoagulants only	1	92	0.001	
IVC filters	0	6	0.60	
Anticoagulants + IVC filter	0	4	0.71	
Thrombolysis	3	7	0.03	
Embolectomy	1	1	0.15	
No treatment	5	5	0.002	

Table 2. Patient Demographics, Comorbidities, Recent Events and Treatment Received

Data are numbers unless otherwise indicated. IVC: inferior vena cava; PE: pulmonary embolism

* P values were calculated by using Student's t-test for continuous variables and the Fisher's exact test for categorical variables

† Mean ± standard deviation

Table 3. Computed Tomography Measurements in Patients with 30-day PErelated Death and Those Without

Measurement/ Score*	30-day PE-related death (n = 10)	No 30-day PE-related death (n = 115)	Р
RVD (mm)	49.3 ± 9.5	45.5 ± 8.6	0.10
LVD (mm)	31.5 ± 6.2	38.1 ± 8.6	0.007
VR	1.6 ± 0.4	1.3 ± 0.5	0.012
Septal deviation [†]	9	68	0.18
Mastora score	43.3 ± 14.9	23.2 ± 20	0.02
Qanadli score	53.5 ± 6.9	31.7 ± 18.3	0.001
Central score	68.3 ± 8	30 ± 26.9	0.001

LVD: left ventricular diameter; PE: pulmonary embolism; RVD: right ventricular diameter; VR: ventricular ratio (RVD/LVD)

* For scores, the values are percentage index [(observed score/maximum score) x 100] and expressed as mean ± standard deviation.

† Number of patients.

Septal deviation is considered present when the interventricular septum is rectilinear or convex towards left ventricle.

significant difference in the clot scores between all-cause 30-day mortality patients and the survivors beyond 30 days. Univariate analysis showed that there was significant difference in all 3 clot scores between patients with 30-day PE-related death outcome and those who did not (P = <0.001-0.02) (Table 3). The LVD and VR were also significantly

different between the two outcome groups, whereas RVD and septal deviation was not significantly different. Correlation between the clot scores and CT measurements of right ventricular dysfunction were moderate and statistically significant (0.35-0.6, P < 0.01).

30-day Mortality

Twenty-three patients died within the 30-day period after CT diagnosis of PE. Ten patients (8%) died of PE. The remaining 13 died from malignancy (n = 9) and complications of sepsis (n=4). PE-related deaths occurred within 5 days in 8 patients and within 30 days in 2 patients. Among those with PE-related death, 5 patients received no treatment, 4 patients received thrombolysis or surgical embolectomy, and 1 patient received anti-coagulation and inferior vena cava filter. The PE-related deaths among the ICU patients were higher than non-ICU patients but was not statistically significant (19.5% vs 5.8%, P = 0.06). All the 3 clot scores were significantly higher in patients with 30-day PE-related death as compared to those who had no PE-related death outcome (P = 0.001 to 0.02). Univariate analysis showed that all clot scores and LVD could predict 30-day PE-related death whereas RVD, septal deviation and VR did not (Table 4). When entered into backward stepwise logistic regression, only central clot score showed significant correlation with 30-day PE-related death (P =

Table 4. Univariate Logistic Regression Analysis for 30-day PE-related Death*

Characteristic	Odds ratio	95% confidence interval	Р
RVD	0.95	0.88-1.02	0.19
LVD	1.09	1.01-1.18	0.02
VR	0.41	0.15-1.1	0.08
Septal deviation	0.16	0.02-1.31	0.09
Mastora Score	0.95	0.92-0.98	0.01
Qanadli Score	0.85	0.75-0.96	0.01
Central Score	0.92	0.87-0.97	0.003

LVD: left ventricular diameter; RVD: right ventricular diameter;

VR: ventricular ratio (RVD/LVD)

*corrected for age and gender

0.003) and other two scores were dropped as non-significant from the model (Table 5).

An elevated central clot score was the strongest predictor of 30-day PE-related death (P=0.003). A central clot index of 53% had 100% sensitivity, 76.5% specificity, 23.5% positive predictive value and 98% negative predictive value for 30-day PE-related death. When patients were stratified as high-risk and low-risk patients based on a cut off central clot index of 50%, 30-day PE-related death could be predicted with 100% sensitivity, 72% specificity, 24% positive predictive value and 100% negative predictive value. The odds ratio was not calculated as all PE-related deaths occurred in one group only and the ratio was infinity.

Discussion

Our study results show that simplified central clot score is a better predictor of 30-day PE-related mortality as compared to the 2 existing scoring systems. This difference may be related to the scoring systems. Mastora score does not extrapolate the embolus burden in the central arteries to the peripheral arteries and gives graded information about residual perfusion. Qanadli score is a semi-quantitative scoring system which gives some information about residual pulmonary perfusion. Central clot score extrapolates the clot burden in the central pulmonary arteries to the periphery and grades them in a 5-point scale. However, the three scoring systems provided highly correlated scores and significant differences were found between clot scores in patients with 30-day PE-related mortality and in those patients without.

It is notable that in this study and in other published series, the majority of patients did not die of acute PE. This probably reflects the efficacy of appropriate anti-coagulation therapy for the vast majority of cases. However, of the 10 patients in our series who died of acute pulmonary embolism, a very high central clot index of 50% was 100% sensitive

Table 5. Prediction of 30-da	y PE-related Death with	Obstruction Scores*
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RSLR* step	PE obstruction score	Р	Odds ratio %	95% confidence Interval
1	Mastora	0.113	0.95	0.9-1.01
1	Qanadli	0.103	1.15	0.97-1.30
1	Central	0.014	1.1	1.02-1.20
2	Qanadli	0.24	1.1	0.94-1.25
2	Central	0.04	1.07	1.0-1.15
3	Central	0.003	1.01	1.03-1.16

LVD: left ventricular diameter; PE: pulmonary embolism; RVD: right ventricular diameter; VR: ventricular ratio (RVD/LVD)

*Weighted retrograde stepwise logistic regression of obstruction scores corrected for age and gender. RVD, LVD, VR and septal deviation were entered at Step 1 and were dropped from next step of analysis as they were not significantly related to the outcome. Note that for each regression step, only central clot scores are highly significant with 95% CI \geq 1 and *P* <0.05 for prediction of 30-day PE death.

for prediction of early death, regardless of the treatment used, and regardless of any other severity findings. It should be noted that in this series, the decision to use aggressive therapies such as intra-arterial thrombolysis or surgical embolectomy was not based on the CT pulmonary artery obstructive indices.

We speculate that since the effective cross-sectional area in the central arteries are smaller than the peripheral arteries, the right ventricular strain may be closely related to the obstruction at the central arteries level rather than peripheral arteries. This probably explains why central clot score is a better predictor of short-term acute PE-related death which is due to acute right ventricular failure.³ Our study results are consistent with those of Engelke et al,11 van der Meer et al¹⁶ and Wu et al¹⁷ who showed that the obstruction scoring using either Mastora or Qanadli systems was a significant predictor of short-term outcome. In another study, Araoz et al¹⁸ did not find any significant association between the clot load determined with the Qanadli system and short-term death due to PE. It appears that the difference between the previous studies on short-term outcome and our study may be related to the differences in patient population. The mean embolic burden was also higher for our patients. Ghaye et al¹² studied 4 scoring systems in their study and found no correlation of clot scores with the outcome. The mean clot load in this study was 52%. In their study, the patients were scanned either on a single slice scanner or multi-detector scanners which might have affected the study results.

The central clot scoring system that we evaluated is a simplified version of the Mastora system, and potentially faster to score. As shown in Figure 1, a high degree of central clot obstruction can be scored on just one image, which makes this potentially a very quick and highly practical



Figs. 1A to 1C. CT pulmonary angiography in a patient with acute PE. Image through the main pulmonary artery and its bifurcation. (A) shows large emboli (small arrows) obstructing the right and left pulmonary arteries. Central clot score at this level is 80. In this case, a single image is sufficient to achieve a central clot score \geq 50. A more caudal section (B) shows multiple emboli in the interlobar and segmental arteries. Mastora score was 56 and Qanadli score was 50 for this patient. (C) Section through the ventricles shows gross dilatation of the right ventricle (RV) with septal deviation to the left (arrow) and reduction in left ventricular (LV) diameter. Ventricular ratio is 1.65. This patient rapidly went into shock and died of acute PE within 6 hours after CT study.

method for junior radiologists and even non-radiologists to score CT scans with a high level of confidence. Several limitations of our study should be considered. First, the study is retrospective and therefore prospective evaluation of the 3 clot scores should be performed in a future study.

Secondly, only 8% of patients had 30-day PE-related mortality. This low mortality rate makes it difficult to accurately predict the clinical impact of this scoring system if it was to be implemented prospectively. Thirdly, more PE-related deaths occurred in patients who did not receive any treatment. These patients were very ill and had other co-morbid conditions which may have affected the outcome in addition to the effect of clot burden.

In conclusion, our study results strongly suggest that a central clot score can predict 30-day mortality due to acute PE and this may form the basis of a larger scale prospective clinical study, and potentially could be valuable as a triage to trigger the early application of aggressive treatments like embolectomy or catheter-directed thrombolysis and clot disruption.

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