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Importance of computed tomography pulmonary angiography for predict 30-day mortality in acute pulmonary embolism patients

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HIGHLIGHTS

- The study provides a cut-off value of RV diameter and CT obstruction index by CTPA to predict acute PE patients' mortality.
- RV diameter of 53 mm or over and CT obstruction index >70 % is associated with increased 30-day mortality in APE patients.
- Increased RV diameter by CTPA is a better predictor of mortality than the clinical Pulmonary Embolism Severity Index (PESI).
- CTPA can be valuable as both the diagnostic and prognostic tool in APE patients.

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ABSTRACT

Objective: The purpose of the present study was to assess the implications of different parameters of computed tomography pulmonary angiography (CTPA) to predict 30-day mortality in acute pulmonary embolism (APE) patients.

Material and Method: Patients who had clinical suspicion of APE and underwent CTPA were recruited in a retrospective cohort study. The findings of the CTPA included the parameters of right ventricular dysfunction (RVD), the severity of obstruction to the pulmonary artery by CT obstruction index, and the ratio of pulmonary trunk diameter and aorta. The endpoint of the study was established as the 30-day mortality associated with APE.

Results: A total of 238 patients with a confirmed APE diagnosis with CTPA were included in the study; 26 (10.9 %) of those patients died within 30 days. In patients with cancer and the Pulmonary Embolism Severity Index (PESI) class 5, the mortality rate was significantly higher. Compared with survivors, the mean CT obstruction index in the non-survivor group was significantly higher ($p < 0.001$). Higher mortality was associated with all RVD parameters identified by CTPA, such as the RV/LV ratio ($p < 0.001$), interventricular septum deviation grade 3 ($p < 0.001$), increased RV diameter ($p < 0.001$), and IVC contrast reflux ($p < 0.001$). The highest adjusted odds ratio was RV diameter at 1.094, followed by PESI and the CT obstruction index at 1.040.

Conclusion: CTPA-detected RVD parameters and CT obstruction index can predict a 30-day mortality rate in APE patients and be used for risk stratification. In APE patients, the RV diameter of 53 mm or greater and the CT obstruction index >70% is associated with increased 30-day mortality.

1. Introduction

Acute pulmonary embolism (APE) is a severe pulmonary and cardiovascular disease with mortality up to 30 %, even after thromboprophylaxis [1,2]. Establishing the risks of adverse outcomes for a patient be capable of therapeutic guide decisions [2–4]. For early diagnosis and proper selection of treatment, risk stratification of APE patients is essential. The adverse APE outcomes are primarily associated with right ventricle pressure overload secondary to acute pulmonary arterial hypertension caused by APE and the development of right ventricular dysfunction (RVD). In hemodynamically unstable patients, echocardiography has been advocated as a first-line imaging modality for

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assessing RVD and promptly initiating fibrinolytic therapy [5,6]. Nevertheless, the operator-dependent and technical challenges of imaging the right heart have limited this modality [7]. As the frontier imaging modality for APE diagnosis [8–11], computed tomography pulmonary angiography (CTPA) has increasingly been established. CTPA provides the advantage of a more comprehensive assessment of the severity of obstruction of the pulmonary artery compared with echocardiography, which can simultaneously diagnose RVD, related underlying pulmonary disease, and other causes of acute chest pain [12,13]. Therefore, CTPA may be a more useful tool for clinical practice to recognize RVD since most patients with suspected APE would undergo CTPA for diagnostic purposes.

Up to the present time, various researchers have suggested several pulmonary embolisms scoring schemes to determine the existence, position, and degree of pulmonary artery obstruction [14–19]. The present study incorporates the Qanadli PE index for the specific assessment and analysis of complete or partial thromboembolism obstruction [16]. The Pulmonary Embolism Severity Index (PESI) was developed in 2005 as a prognostic-predictive index, which has been shown to have high predictive accuracy [17,18]. Nevertheless, PESI does not incorporate RV dysfunction, which in the appraisal is associated with adverse effects. The use of alternative scoring systems considering the presence of RV dysfunction as a predictive factor has been proposed by current guidelines [19]. The objective of this study is to evaluate the importance of CTPA risk stratification parameters to predict 30-day mortality in APE patients and to determine whether each CTPA finding predicts mortality independently of the Pulmonary Embolism Severity Index (PESI).

2. Materials and methods

2.1. Patient population

This study was a retrospective cohort study conducted at Khon Kaen University, Khon Kaen, Thailand. Between January 2015 and December 2019, consecutive adult patients diagnosed with CTPA as APE were enrolled in the study. The exclusion criteria were those with unsatisfactory CTPA quality, incomplete medical records, or CTPA contraindication, including renal failure or history of allergic reactions to contrast agents containing iodine. Eligible patients were followed up and monitored for mortality for a duration of 30 days (Fig. 1). This study was reviewed and proved by the local Ethics Committee of Khon Kaen University, Thailand, and was registered under reference number HE631656. The patient consent form was waived due to the retrospective study design. All methods were performed following the relevant guidelines and regulations. The results of this study are reported anonymously and in compliance with the Declaration of Helsinki.

2.2. Clinical data collection

To obtain their demographic data, underlying condition, and vital signs regarding heart rate, systolic blood pressure, respiratory rate, temperature, oxygen saturation, and the patients' medical record was carefully reviewed. Patients were consequently categorized into five PESI categories, including Class I (< 65 points: very low risk), Class II (66–85 points: low risk), Class III (86–105 points: intermediate risk), Class IV (106–125 points: high risk) and Class V (> 125 points: very high risk), as well as the total PESI score, was assessed [17]. Survival activity was determined at 30 days on both inpatient and outpatient follow-up.

2.3. Computed tomography pulmonary angiography (CTPA) scanning protocol

CTPA was performed on either a 128-slice MDCT (Brilliance 128, Philips Healthcare, Netherlands) or a dual-source CT scanner (Somatom Definition; Siemens Healthcare, Forchheim, Germany). During a single breath-hold, 2 cm below the top of the diaphragm to a level just above

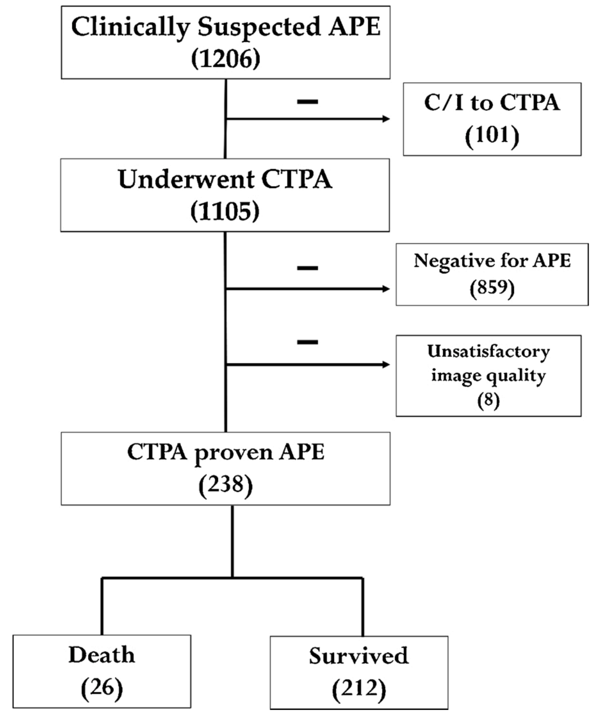

Fig. 1. Flow-chart of the patients' inclusion in the study.
(CTPA: Computed tomography pulmonary angiography, C/I: Contraindication, APE: Acute pulmonary embolism).

the aortic arch, the caudocranial spiral volumetric acquisition was accomplished. The image acquisition parameters were 0.33 millisecond gantry rotation time, 0.6 mm collimation with z-flying focal spot technique, 120 kV, automated adjusted mA depend on body size, 1.2 pitch, and 0.6 mm reconstructed section thickness. A 1.5 mL/kg bolus of iodinated contrast material (350 mg/mL, Omnipaque; GE Healthcare) was injected at 4 mL/seconds with a dual-head power injector, followed by a 10−20 ml saline flush at the same rate as the contrast injection to achieved contrast medium enhancement and decreased streak artifact from superior vena cava. Bolus tracking systems were used to start the scan with the region of interest positioned at the main pulmonary artery. For triggering data acquisition, automated bolus triggering was used with a region of interest in the main pulmonary artery and a threshold of 100 HU. When a pre-determined threshold is reached, scanning begins, with a delay allowing optimal pulmonary artery opacification. The images were obtained at standard mediastinal settings (window width, 350 HU; window level, 50 HU) and lung settings (window width, 1500 HU; window level, 500 HU).

2.4. CTPA imaging analysis

The images of patients with a positive APE diagnosis were chosen and reviewed retrospectively at an independent workstation in arbitrary order by two experienced cardiovascular and thoracic radiologists (NC and WS). Both were unaware of the patient's condition at the time of initial presentation and the clinical outcome. The arterial tree of each lung was perceived as having ten segmental arteries to establish the CT obstruction index (Qanadli PE index) (three to the upper lobes, two to the middle lobe and the lingula, and five to the lower lobes). One point was scored for the presence of embolus in a segmental artery, and a value equal to the number of segmental arteries occurring distally was scored for embolus at the most proximal arterial level. A weighting factor was applied to each value, based on the degree of vascular obstruction, to provide additional details on the residual perfusion distal to the embolus. When no thrombus was detected, this particular aspect was equal to zero; 1, when partial occlusive thrombus was observed; or 2, with total occlusion (Fig. 2). Therefore, the score of 40 and 100 percent per patient was the maximum CT obstruction index. The isolated subsegmental embolus was considered a segmental artery partially occluded and given a value of 1. By dividing the patient score by the overall total score and multiplying the result by 100, the CT obstruction index percentage was determined [16]. In the present study, several parameters were evaluated for RVD on CTPA as follows; increased RV diameter, increased RV/LV ratio, interventricular septum deviation, or IVC contrast reflux. The RV/LV ratio was assessed at the widest point between the inner surface of the free wall and the surface of the interventricular septum by measuring the minor axes of the right and left ventricles of the heart in the transverse plane (Fig. 3). Then the ratio of RV/LV was determined [11,12]. Interventricular septal deviation was measured on a 3-point scale: 1 = normal septum (convex to the right ventricle); 2 = flattened septum; and 3 = convex septal deviation to the left ventricle (Fig. 4) [20,21]. Backflow reflux of contrast media into IVC was also evaluated and verified as positive or negative (Fig. 5). At a single predefined transverse scanning level, the diameters of the main pulmonary artery and ascending aorta were determined at the point at which the right pulmonary artery is in continuity with the main pulmonary artery and sweeps through the midline. The diameter ratio of the pulmonary artery to the ascending aorta was then evaluated [22].

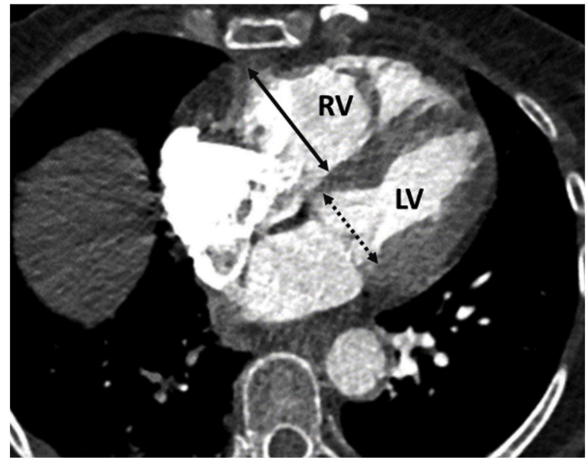

Fig. 3. Measurement of RV and LV diameter on axial CTPA image. The ventricular diameters were determined by identifying the maximum distance perpendicular to the long axis of the heart between the ventricular endocardium and the interventricular septum. The RV/LV ratio was then calculated. (CTPA: Computed tomography pulmonary angiography; RV: right ventricle; LV: left ventricle).

2.5. Statistical analysis

Patients were divided into two groups according to the 30-day mortality outcome: survivors and those who died. Descriptive statistics compared clinical variables of the groups. To compare variations in numbers and proportions, respectively, Wilcoxon rank-sum and Fisher's exact tests were used between the two classes. Two-sided p-values were being used to test the significance of differences; a *p*-value <0.05 was assumed to be statistical significance. Mortality-related factors were determined by logistic regression analysis. Univariate logistic regression analyses were used to calculate the unadjusted odds ratio (OR) for and variable for mortality. In subsequent multivariate logistic regression analyses using a stepwise approach, all variables with $p < 0.20$ in univariate analysis, obstructive index, and PESI score were included. In terms of unadjusted OR, adjusted OR, and 95 percent confidence interval (CI), analytical results were presented. To determine the performance of fit of the final predictive model, the Hosmer-Lemeshow method was used. We have determined the cut-off value of significant numerical variables to predict mortality. Interobserver reproducibility was assessed using unweighted kappa statistics for the evaluation of the CTPA parameters. The agreement's kappa value was perceived as: poor, < 0.20; fair, 0.21– 0.40; moderate, 0.41–0.60; good, 0.61–0.80; and excellent, 0.81–1.00 [23]. An agreement between the two observers was evaluated using the intraclass correlation coefficient (ICC) for continuous variables, and the intraobserver and interobserver agreement was evaluated using the Bland-Altman method [24]. All the statistical analysis was conducted on Microsoft-excel spreadsheets, Microsoft Windows Statistical Package for Social Sciences Applications (SPSS), Version 20.0 (IBM Corp., Armonk, NY, USA), and version 15 of the STATA Software Programs (StataCorp, College Station, TX, USA).

3. Results

Two hundred thirty-eight consecutive APE patients accomplished the inclusion criteria of the study. Among all, 26 patients died within 30 days (10.9 %). In both groups, there was no significant difference in age and sex. Those who died had a higher proportion of cancer, abnormal vital signs, reduced oxygen saturation, class 5 PESI, and RV strain ECG

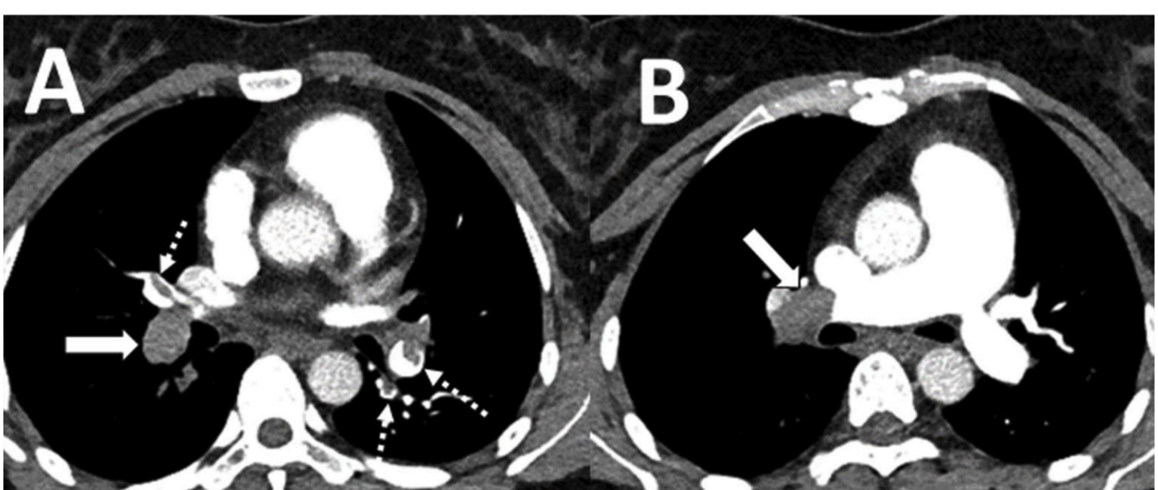

Fig. 2. Axial CTPA demonstrations occlusive clot in the right main pulmonary artery (A and B: solid arrows) scored by two radiologists as weighting factor of 2 and partially occlusive clot in left basal segmental arteries (A: dashed arrows) scored by two radiologists as weighting factor of 1. CT obstruction index scored by two radiologists is 55 %. (CTPA: Computed tomography pulmonary angiography).

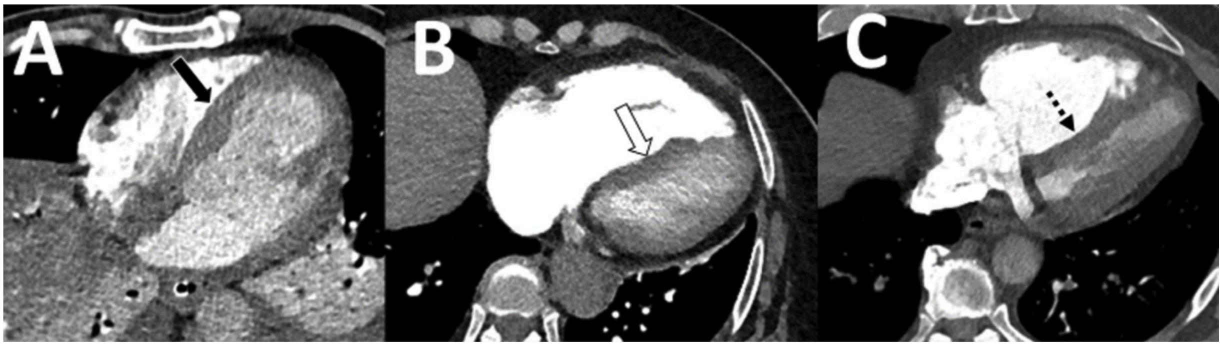

Fig. 4. Deviation of interventricular septum was evaluated on a three-point scale: 1 = normal septum (A : black arrow); 2 = flattened interventricular septum (B : white arrow); and 3 = septum deviation convex toward the left ventricle (C : dashed arrow).

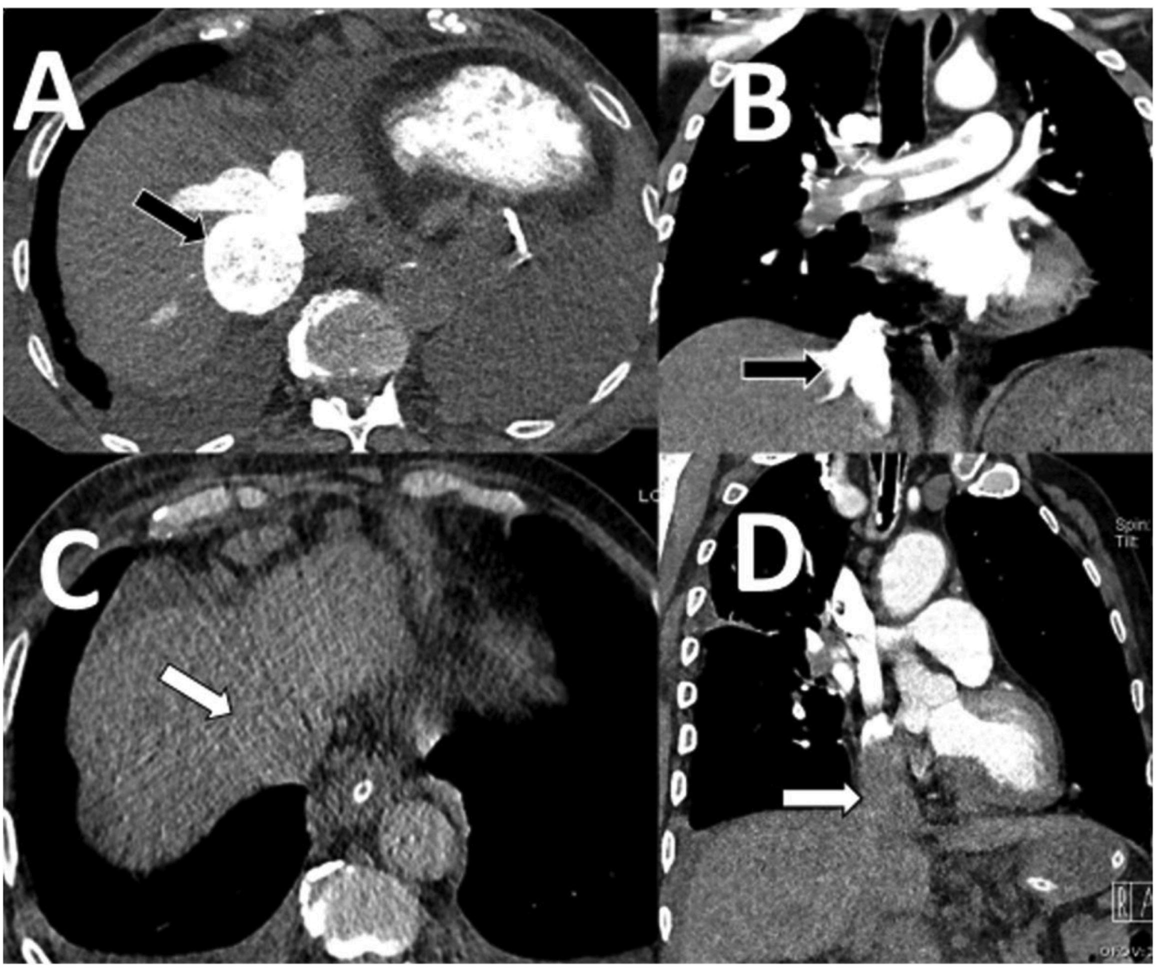

Fig. 5. Backflow reflux of contrast media into IVC and verified as positive (A and B: black arrows) or negative (C and D: white arrows). (IVC: inferior vena cava).

than the surviving group (Table 1). The death group's PESI score was significantly higher than in the surviving group (135 vs. 96; $p < 0.001$). The interobserver reproducibility for measured RV diameter and CT obstruction index was excellent concerning the CTPA parameters (ICC=0.997; 95 %CI 0.91−0.998 and ICC=0.984; 95 %CI 0.91−0.991, respectively). The intraobserver variability was small for measuring RV diameter and CT obstruction index with the ICC ranging from 0.973 to 0.98. The Bland-Altman plot revealed strongly agreeing interobserver and intraobserver measurements of RV diameter with mean difference = -0.25 (95 %CI 0.78 to -0.83), and -0.2 (95 % CI 1.85 to -1.89), respectively. Most of the RV diameter data are within the agreement limit between interobserver and intraobserver (92.68 % and 97.56 %, respectively) (Fig. 6). The agreement between interobserver for IVC contrast reflux was good (κ = 0.76; CI, 0.48–0.94) and moderate for interventricular septum (κ = 0.58; 95 % CI, 0.19–0.76). All CTPA parameters except grade 2 interventricular septal deviation or flattened interventricular were significantly different between both groups (Table 1). The RV diameter was significantly larger in the death group than the survived group (57.2 mm vs. 40.9 mm; $p < 0.001$).

There were three remaining factors to predict the 30-day mortality in APE patients (Table 2). RV diameter had the highest adjusted odds ratio at 1.094, followed by PESI and obstructive index at 1.040 (Table 2). The

Table 1
Baseline characteristics, physical signs, and computed tomography pulmonary angiography (CTPA) parameters of patients with acute pulmonary embolism categorized by survival outcome.

Factors	Survived N = 212	Death N = 26	*p*-value
Age, years	59 (21-84)	59 (35-86)	0.727
Male sex, n (%)	122 (57.55)	11 (42.31)	0.149
Comorbid diseases, n (%)			
Cancer	58 (27.36)	13 (50.00)	0.023
Heart failure	17 (8.02)	2 (7.69)	0.999
Lung disease	33 (15.57)	6 (23.08)	0.397
Surgery/trauma	33 (15.57)	6 (23.08)	0.397
Vital signs, n (%)			
Heart rate ≥ 110/min	66 (31.13)	18 (69.23)	< 0.001
Respiratory rate ≥ 30/min	78 (36.79)	17 (65.38)	0.010
Temperature < 36 °C	2 (0.94)	4 (15.38)	0.001
Oxygen saturation < 90%	118 (55.66)	23 (88.46)	0.001
ECG RV strain pattern, n (%)	26 (12.26)	17 (65.38)	< 0.001
PESI	96 (37-166)	135 (80-189)	< 0.001
PESI classification, n (%)			
1	31 (14.62)	0	0.037
2	54 (25.47)	1 (3.85)	0.014
3	37 (17.45)	2 (7.69)	0.21
4	48 (22.64)	8 (30.77)	0.36
5	42 (22.68)	15 (57.69)	< 0.001
CTPA parameters			
RV diameter (mm)	40.9 (22.1-68.3)	57.2 (47.8-67.8)	< 0.001
LV diameter (mm)	38.2 (18.6-60.5)	29.3 (18.9-44.3)	< 0.001
RV/LV ratio	0.99 (0.58-2.54)	1.93 (1.20-3.23)	< 0.001
PA/Ao ratio	0.94 (0.67-2.37)	1.05 (0.85-2.10)	0.004
CT Obstruction index	25 (5-100)	78(50-100)	< 0.001
Interventricular septum, n (%)			
Normal	109 (51.42)	0	< 0.001
Grade 2	72 (33.96)	8 (30.77)	0.829
Grade 3	31 (14.62)	16 (61.54)	< 0.001
IVC contrast reflux	39 (18.4)	18(69.2)	<0.001

Note. Data presented as median (range) unless indicated otherwise; PESI: Pulmonary Embolism Severity Index.

final model had a Hosmer-Lemeshow chi-square of 4.25 ($p = 0.833$). Among predictors, RV diameter had the highest area under the ROC curve at 93.80 % (95 % confidence interval of 90.46 %–97.14 %). RV diameter of 53 mm or over had sensitivity and specificity of 80.77 % and 85.85 %, while CT obstructive index of 70 or over had sensitivity and specificity of 80.77 % and 84.43 % (Fig. 7). In comparison, the PESI of 111 or over had sensitivity and specificity of 80.77 % and 67.45 %, with the lowest lower area under ROC of 82.21 % (Fig. 7).

4. Discussion

The current retrospective cohort study revealed that the APE mortality rate was 10.9 % over 30 days, comparable to other studies [25–27]. The cause of death in patients with APE is usually acute right heart failure [1,2,6,26]. Acute PE raises the pulmonary arterial system pressure following RV dysfunction, which might contribute to right

Table 2
Factors associated with mortality in patients with acute pulmonary embolism.

Factors	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
RV diameter	1.344 (1.200, 1.506)	1.094 (1.007, 1.188)
CT Obstruction index	1.081 (1.050, 1.113)	1.040 (1.003, 1.079)
PESI	1.051 (1.030, 1.072)	1.040 (1.015, 1.066)

Note. A model was adjusted for RV dysfunction parameters, LV diameter, RV/LV ratio, PA/Ao ratio; RV: right ventricle; CT: computed tomography; PESI: Pulmonary Embolism Severity Index.

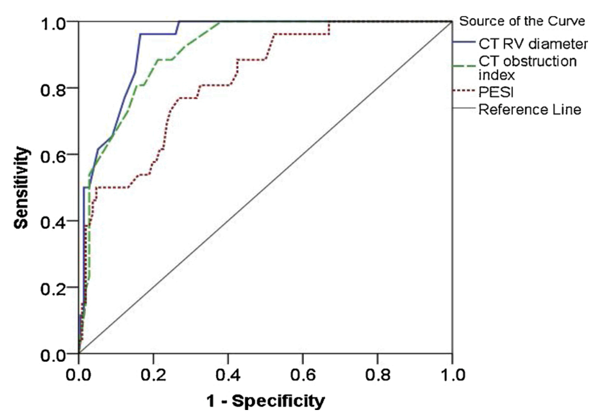

Fig. 7. The receiver operating characteristic (ROC) curves of right ventricular diameter from CTPA (solid blue line), CT obstruction index (dashed green line), and PESI (dotted red line) on mortality in patients with acute pulmonary embolism.
(CTPA: Computed tomography pulmonary angiography; PESI: Pulmonary Embolism Severity Index). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

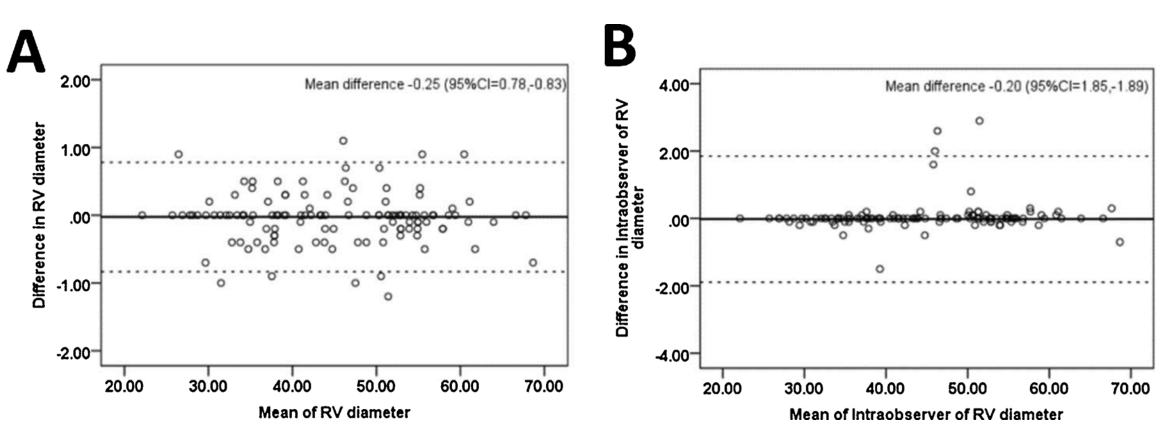

Fig. 6. Bland-Altman plots show a good interobserver measurement of right ventricular diameter (A) and excellent intraobserver measurement of RV diameter (B).

heart failure and circulatory collapse [27–29]. There is a higher mortality rate among patients with RV dysfunction than those without RV dysfunction, even though they are initially hemodynamically stable [27–29]. In patients with APE, the presence of RV dysfunction is, therefore, a predictor of adverse clinical outcomes [26,28,29]. RV diameter had the highest adjusted odds ratio among the independent factors for APE mortality prediction (Table 2). At 1.040, the other two variables had a comparable adjusted odds ratio. These data may imply that RV size is the strongest predictor compared with the other parameters. As mentioned earlier, the RV size is related to right ventricular dysfunction from APE, which is an indicator of mortality independent of hemodynamic status or PESI score [27–29].

CTPA's measured RV diameter has an excellent interobserver agreement (ICC = 0.997; 95 %CI 0.91−0.998); therefore, CTPA has a measurable and reproducible RV size assessment. This finding is agreeable with the recent ESC guideline-recommended using RV diameter and RV/LV ratio either by echocardiography or CT to evaluate further intermediate-risk patients stratified by clinical parameters [28]. We also discovered excellent agreement between interobserver for evaluated CT obstruction index; hence, CT obstruction index on CTPA also offers a reproducible and quantitative assessment of APE [16,30].

The present study's CT obstruction index is higher in the non-survivor group, following previous studies [31,32]. In real-world practice, the risk calculations are based on the pulmonary embolism severity index (PESI) and are recommended to guide management accordingly [17]. Adjusting for the existence of RVD can be performed for the vast intermediate-risk population, categorizing patients as intermediate/high risk or intermediate/low risk as assessed by the proposed parameter from CTPA. Nevertheless, the PESI and CT obstruction index should be considered along with the RV diameter to estimate the 30-day mortality in APE.

Our study's main strength is that imaging data and clinical outcomes were assessed blindly for treatment and outcome. In addition, we evaluated the CTPA parameters most frequently utilized, and our results provided a cutoff point for each independent predictor. Clinicians could predict the 30-day mortality of individuals with the sensitivity and specificity provided. For an excellent interobserver agreement, these CTPA parameters are feasible since these parameters would be less user-dependent and more reproducible.

The present study's limitations are retrospective design and single-center, which weaken generalizability. Finally, the present study did not include the cardiac biomarkers such as BNT or NT-pro BNP because additional assessments from the cardiac biomarkers are often not carried out in our everyday practice. Despite the promising results regarding the mortality prediction, further prospective cohort studies are needed to validate our results.

5. Conclusion

A better mortality predictor than the PESI classification is increased RV diameter. In APE patients, an RV diameter of 53 mm or more and a CT obstruction index >70% are associated with increased 30-day mortality. Since CTPA is the best modality for diagnostic APE, simultaneous evaluation of the cardiac chambers is a practical and straightforward way of evaluating right ventricular dysfunction. CTPA can be valuable as both a diagnostic and prognostic tool in APE patients.

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Intellectual property

The authors confirm that they have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, concerning intellectual property. In so doing, they confirm that we have followed the regulations of our institutions concerning intellectual property.

Authorship

The authors meet the ICMJE criteria. They attest that all authors contributed significantly to creating this manuscript, each having fulfilled criteria as established by the ICMJE.

The authors confirm that the manuscript has been read and approved by all named authors.

The authors confirm that all named authors have approved the order of authors listed in the manuscript.

CRediT authorship contribution statement

Narumol Chaosuwannakit: Conceptualization, Methodology, validation, formal analysis, investigation, data curation, writing-original draft, writing-review & editing, supervision, Proof the final manuscript. **Wannaporn Soontrapa:** Interobserver CTPA interpretation, writing-review & editing original draft, Proof the final manuscript. **Pattarapong Makarawate:** Resources, writing-review & editing original draft, Proof the final manuscript. **Kittisak Sawanyawisuth:** Statistical analysis, writing the original draft, Proof the final manuscript.

Availability of data and materials

Data sharing did not apply to this article.

Ethics approval and consent to participate

This study was reviewed and proved by the local Ethics Committee of Khon Kaen University, Thailand, and was registered under reference number HE631656. The patient consent form was waived due to the retrospective study design. All methods were performed following the relevant guidelines and regulations. The results of this study are reported anonymously and in compliance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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