Quantitative evaluation of computed tomography findings in patients with pulmonary embolism: the link between D-Dimer level and thrombus volume

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SUMMARY

OBJECTIVE: To investigate the correlation of D-dimer levels and computed tomography properties of pulmonary embolism.

METHODS: A total of 58 treated patients with diagnosis of properties of pulmonary embolism were retrospectively studied. All patients underwent a D-dimer blood test. In computed tomography images, septal angle, interventricular septal thickness, and the diameters of all cardiac chambers and pulmonary arteries were measured. The thrombus volume (load) and density at all pulmonary arteries (main, right, left pulmonary arteries, and segmental arteries) were calculated.

RESULTS: A significant correlation was found between D-dimer and total thrombus volume (p=0.009, r=0.342). Total thrombus volume and total thrombus density were calculated with mean value of 23.40±60.63 ml and 66.16±38.48 hounsfield unit (HU), respectively. Right ventricle/left ventricle ratio showed positive correlation with the D-dimer level (p=0.02).

CONCLUSION: Increased D-dimer levels with RV/LV ratio and their correlation with total thrombus volume suggest that it may be a prognostic factor.

KEYWORDS: Thrombosis. D-dimer. Pulmonary embolism. X-Ray computed tomography. Quantitative analysis.

INTRODUCTION

Pulmonary embolus (PE) refers to obstruction of the pulmonary artery or one of its branches by material (*e.g.* thrombus, tumor, air, or fat) that originated elsewhere in the body. Acute PE is a common and fatal disease whose mortality rates can be as high as 31 to 58% when shock is present[1]. It increases the pressure of the pulmonary arterial system and right ventricle (RV), resulting in RV dysfunction, which may progress to right heart failure and circulatory collapse[2,3].

Difficulty may occur in diagnosis due to its clinical nonspecific nature and presentation with different clinical situations. Initiation of the treatment just after immediate diagnosis provides a decrease in morbidity and mortality.

Patients can be classified as massive and sub-massive according to their hemodynamic stability. For the confirmation of the probability of PE, D-dimer level is the most commonly used laboratory parameter in routine clinical practice. D-dimer is formed upon breaking down the cross-linked fibrin. In patients with suspected PE, blood D-dimer levels correlate with the probability of having PE[4,5].

As an imaging modality, computed tomographic pulmonary angiography (CTPA) is the frontline imaging modality in the patients with suspected acute PE[6,7]. CTPA is an essential component in commonly used clinical diagnostic algorithms with the highest sensitivity (83%) and specificity (96%)[8]. PE clot volume can be measured in CTPA setting using a semi-automated algorithm[9].

To the best of our knowledge and the literature, there is no study correlating total thrombus volume (TTV: the thrombus load in the main and both pulmonary arteries including segmental branches) with D-dimer level.

The objective of this article was to investigate the correlation of D-dimer level and CT properties of thrombosis such as TTV and RV/left ventricle (LV) ratio.

METHODS

Study population

Between May 2016 and May 2019 in the hospital of the institution, in a total of 58 patients treated with the diagnosis of PE, were studied retrospectively. All patients had D-Dimer blood test. Patients with inadequate quality of CT images or insufficient breathing during CT scanning, patients with chronic diseases (malignancy, cardiac insufficiency or chronic cardiac diseases), and those under 18 years of age were excluded from the study.

Patients between 18-65 years of age with optimum CTPA image quality and breathing, patients clinically and radiologically diagnosed with PE, were enrolled in the study.

The study protocol was approved by the institutional ethics review committees (approval number: 2019.191.10.12).

Computed tomography pulmonary angiography acquisition

A 128-row multi-detector CT scanner (Aquilion™ Prime; Canon Medical Systems) was used for CTPA scanning. Field of view (FOV) of the whole chest was scanned from the lung apex to the diaphragm with a single breath-hold.

Computed tomography protocol

CT acquisition was done by the following parameters: the current of 100–250 mAs modulated by personal body mass index dose; tube voltage of 100–140 kV and collimation of 0.5 mm x 80, gantry rotation time of 0.35 sec, pitch factor of 0.813, FOV: 20x20 cm, slice thickness of 1 mm, and slice interval of 0.8 mm. For intravenous bolus injection of non-ionic contrast material (350 mg/100 mL, Iohexol, Omnipaque®; GE Healthcare, Cork, Ireland), a mechanical injector was used at a flow rate of 4.5–5.0 mL/sec. The automatic bolus-tracking method was used with the ROI (region of interest) positioned at the level of the main pulmonary artery with a pre-defined threshold of 100 HU, and a fixed delay of 5 sec was used for data acquisition. Electrocardiogram (ECG)-gating technique was not performed. Patients with good quality of images, without artifacts, and those the largest ventricular diameters were enrolled in the study. Cardiac measurements were made in the

phase where the largest ventricle diameters were thought to be in the diastolic phase.

Imaging review

An eight-year-experienced radiologist assessed the patients for the presence of PE and analyzed the distribution within the main pulmonary vasculature and segmental arteries bilaterally.

After acquisition, the obtained CTPA images were transferred to Picture archiving and communication system (PACS) (Sectra 7.0, Sectra AB, Linköping, Sweden) and were analyzed at the workstation (Vitrea 2 workstation; Vital Images, Minnetonka, MN, USA).

Interventricular septal angle, thickness, and the diameters of all cardiac chambers in a four-chamber plane (4CH) (Figure 1); and the diameters of main, right and left pulmonary arteries were measured on the axial CT images (Figure 2). The thrombus volume (load) and density at all pulmonary arteries (main, right, left pulmonary arteries, and segmental arteries) were calculated (Figure 3). Determination of the boundaries of the thrombus (seen as an intraluminal filling defect in CTPA) was made using semi-automated (a pixel-based image segmentation method known as region growing algorithm) and manual
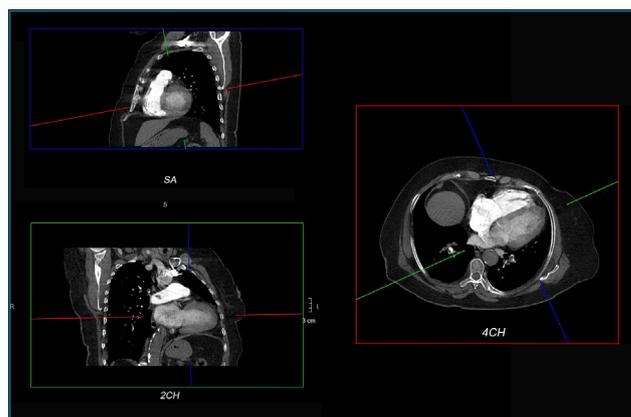
Figure 1. Shows cardiac planes including four-chamber (4CH; including both atria and ventricles), two-chambers (2CH, one atrium and ventricle) and short axis (SA, just both atria or ventricles).
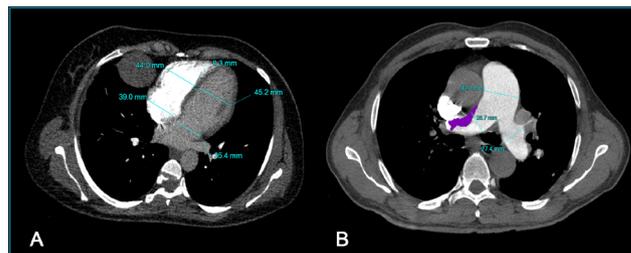
Figure 2. The measurements of cardiac chambers at 4CH plane (A) and pulmonary arteries (B) are shown. The thrombus area at right pulmonary artery (B).

drawing tools. The measurements of thrombus volume were categorized into five subgroups including the main pulmonary artery (PA), right PA, left PA, right lung thrombus volume (upper, middle, and lower lobe segmental arteries), and left lung thrombus volume (upper and lower lobe segmental arteries).

The diameter of cardiac chambers was performed between the two endocardia. Interventricular septal angle measurement due to calculation method defined by Tang et al. was done in axial CT images[10]. The angle between the connecting line from the midpoint of the sternum to the thoracic vertebral spinous process and interventricular septum (Figure 4).

Laboratory tests

In all patients, complete blood count (hemoglobin, hematocrit, neutrophil, leukocyte, and platelet), C-reactive protein, and D-dimer level were analyzed.

Statistical analysis

All data were analyzed using a statistical package program (SPSS version 17.0; SPSS, Inc., Chicago, IL, USA). The variables were investigated using visual (histograms and probability plots) and analytical methods to determine whether they are normally or not normally distributed. Investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Spearman test. A 5% type-1 error level was used to infer statistical significance.

RESULTS

In a total of 58 cases, 22 were males (37.9%) and 36 females (62.1%), with a mean age of 60.14 years (minimum 20 years, maximum 93 years).
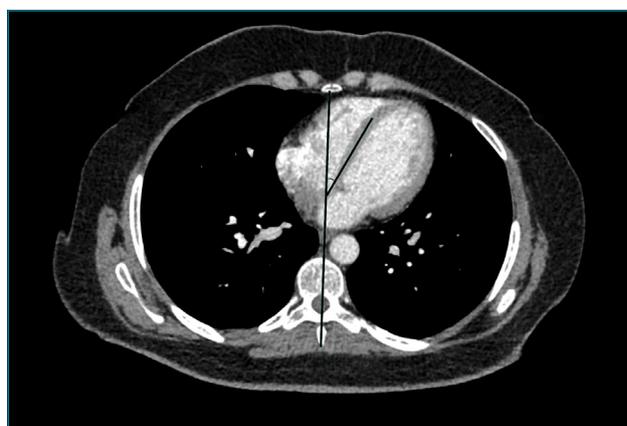
There was a significant correlation between D-dimer and TTV in the Pearson correlation test (p=0.009, r=0.342). D-dimer level was ranging between 0.16 and 22.94 (mean value 6.16±5.04). TTV and total thrombus density (TTD) were calculated with a mean value of 23.40±60.63 ml (min: 1.46 mL, max: 404.12 ml) and 66.16±38.48 HU (min: -67.70 HU, max: 213.50 HU), respectively (Figure 5). TTD was automatically calculated at the workstation (Vitrea 2 workstation; Vital Images, Minnetonka, MN, USA) when the volume was measured (Figure 1). Demographic properties and CT measurement values of the study population are shown in Table 1.

The thickness of the interventricular septum was measured with the mean value of 13.46±11.64 mm.

Interventricular septal angles were measured as 47.88±22.00 degrees. There was no statistically significant correlation between angles and TTV.
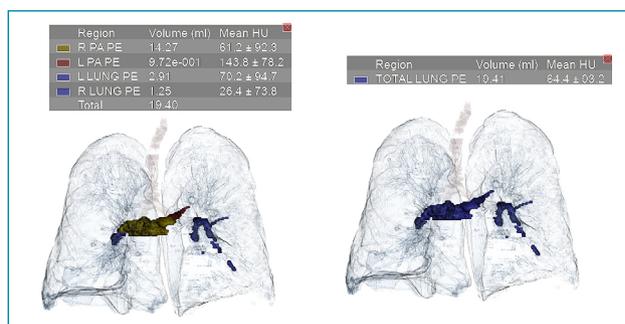
Figure 3. The measurement of thrombus volume (load) and density at main, right, left pulmonary arteries are shown. The thrombus volume of segmental arteries in both lungs is defined as lung PE (A). Total thrombus volume and mean density of total thrombus volume (B).

Figure 4. The angle between the connecting line from the midpoint of the sternum to the thoracic vertebral spinous process and interventricular septum.
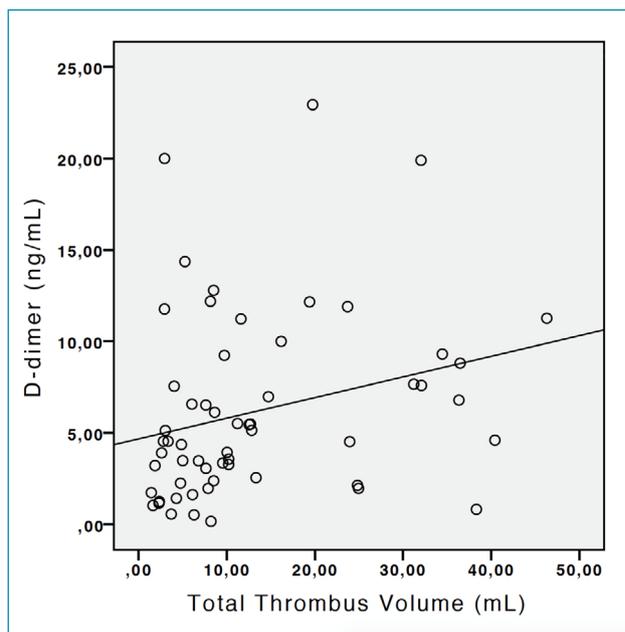
Figure 5. Shows a significant correlation between D-dimer and total thrombus volume (p=0.009, r=0.342).

In the non-parametric Spearman test, there was a significant correlation between D-dimer and TTV (p=0.009). A significant correlation was found between TTV and the hematocrit level (p=0.034) as well as C-reactive protein (CRP) (p=0.044).

Interventricular septal angle, and left atrium (LA) and right atrium (RA) diameter showed a significant correlation with TTLV (p=0.023, p=0.037, and p=0.002, respectively).

RV/LV ratio showed positive correlation with the D-dimer level (p=0.02).

DISCUSSION

In PE, although the diagnosis is based on clinical findings, laboratory and imaging findings are crucial. The amount, the location of the thrombus, and the degree of obstruction affect survival[11,12]. In our study, RV/LV ratio showed positive correlation with D-dimer level and a significant correlation was found between D-dimer and TTV.

In some studies, thrombus load has been shown to be predictive of mortality and determination of hemodynamic severity in patients with acute PE[13,14]. By using measurement parameters (including vascular obstruction, RV/LV ratio, minimum LV diameter, and diameter of the central PA), the thrombus load can be evaluated in the determination of hemodynamic severity[14]. Also, quantitative cardiac CT measurements obtained on axial CT images (RV short axis, LV short axis, and particularly the RV/LV short axes ratio) have shown a significant positive (RV short axis, RV/LV diameter ratio) or negative (LV short axis) correlation with the severity of PE[14] or with fatal outcomes[15,16].

Table 1. Demographic properties and CT measurement of the study population.

	Unit	Value
Age	years	60.14±17.92
Female	n (%)	36 (62.1)
White blood cell count	x10⁹/L	9.4±4.4
D-dimer	µg/mL	6.11±5.05
CRP	mg/dL	63.06±88.94
Platelet	x10³/mL	251.8±101.01
PDW	%	15.15±3.28
TTV	mL	23.40±60.64
TTD	HU	66.17±38.49
Interventricular septum thickness	mm	13.47±11.65
Septal angle	degree	151.88±22.00

TTV: total thrombus volume, TTD: total thrombus density, CRP: C-reactive protein, PDW: platelet distribution width.

The results of the studies of patients with PE revealed that signs of RV strain at CTPA (RV/LV diameter ratio >1, leftward septal bowing) had a sensitivity of 78–92%, specificity of 100%, and positive predictive value of 100% comparing to echocardiographic findings for the detection of RV dysfunction. Other studies predicted a severe PE when the RV/LV diameter ratio was more than 1.5[14-16]. In the current study, the diameter ratio of RV/LV in 29 of 58 patients (50%) with mean value was calculated as 1.17±0.48. RV/LV ratio also correlated with D-dimer level. Therefore, increased D-dimer level may indicate an increase in right ventricular tension.

An RV/LV diameter ratio calculation on 4CH CT images greater than 0.9 has been shown to have association with a sensitivity of 83% and specificity of 49% for predicting the occurrence of adverse clinical events (for example 30-day mortality or the need for cardiopulmonary resuscitation, mechanical ventilation, vasopressors, thrombolysis, or embolectomy)[17]. Schoepf et al. reported a higher mortality rate in patients with increased RV/LV diameter ratio of more than 0.9 compared to not increased or equal to 0.9, calculated in PE patients on 4CH images. RV enlargement had a sensitivity, specificity, positive predictive value, and negative predictive value of 78.2, 38, 15.6, and 92.3%, respectively, for prediction of 30-day mortality[18].

Similarly, to our study, Kaufman et al. evaluated the reproducibility of PE clot volume quantification using CTPA in a multicenter setting. They used anonymized CTPA data of 23 patients acquired from 23 scanners of 18 imaging centers. Two independent analysts measured PE volumes using a semi-automated region growing algorithm. TTV was calculated per patient as the primary endpoint and individual thrombus volume (ITV), Qanadli score, and modified Qanadli score per patient as secondary endpoints. Inter- and intra-observer reproducibility were evaluated using intra-class correlation coefficient (ICC) and Bland-Altman analysis. As results, clot volumes ranged from 0.0041–47.34 mL (mean±SD, 5.93±10.15 mL), found by Analyst 1. On the second read, analyst 1 found the same number and distribution of emboli with a range of volumes for read 2 from 0.0041–45.52 mL (mean±SD, 5.42±9.53 mL). For Analyst 2, thrombus volumes ranged from 0.00459–46.29 mL (mean±SD, 5.91±10.06 mL). Inter- and intra-observer variability measurements indicated excellent reproducibility of the semi-automated approach for quantifying PE volume load. ICC for all endpoints was greater than 0.95 for inter- and intra-observer analysis. No significant biases were indicated by Bland-Altman. They concluded that, the semi-automated region growing algorithm for quantifying PE was a suitable method for image analysis in multi-centered clinical trials and was reproducible using data from multiple scanners[9]. By the methodology used in the study,

they mentioned that the changes in absolute thrombus volume greater than about 2 mL or 5% regardless of the starting size of the clots, should be pick up. This could be helpful to estimate sample size requirements for clinical trials using clot burden quantification as an endpoint in PE treatment studies. In the present study, the mean value of TTV was measured as 23.40±60.63 mL.

The current study was designed as a retrospective study and the patients enrolled were those with acute onset PE. Measurements were only performed on CTPA images statically, no dynamic investigation method was used in the current study such as wall motion abnormality and ejection fraction calculation in ECG or pulmonary wedge pressure at pulmonary catheter angiography. The acquisitions were not done with ECG-gating method.

D-dimer becomes active after 24–48 hours and then decreases. It may decrease after the patient applies to the hospital; thus, a low D-dimer level might have been analyzed. In this retrospective study, although TTV correlates with D-dimer level, larger prospective studies are needed.

There are some limitations in the in the current study. Firstly, the only diametric measurements of the cardiac chambers were performed in 4CH plane and the ratio of RV/LV was calculated. Measurements of the thrombus volume and determination of its borders were made in contrast enhanced images using semi-automated method and manual drawing option; the thrombus volume in the right, left, and total lungs were calculated, though not separately in segmental branches by lobe. Therefore, the measured thrombus could show variations in density. Secondly, due to the retrospective design nature of the study in the emergency condition, the acquisitions were not performed by ECG-gating method and the cardiac measurements were done at a single cardiac phase. The images with the largest ventricle diameter at diastolic phase were selected for the evaluation. However, it could be better to do it with ECG-triggering technique.

CONCLUSIONS

Many studies showed thrombus volume to not be a significant determinant of outcomes; rather, the right heart strain is the best predictor. On the other hand, the current study showed TTV and RV/LV ratio had a positive correlation with increasing D-dimer level. Therefore, increased D-dimer levels with RV/LV ratio and their correlation with TTV suggest that it may be a prognostic factor, but larger prospective studies are needed to reveal this more clearly.

AUTHORS' CONTRIBUTIONS

HS: Conceptualization, Data Curation, Writing – Original Draft, Writing – Review & Editing. **LCM:** Conceptualization, Formal Analysis, Writing – Review & Editing.

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In the manuscript "Quantitative evaluation of computed tomography findings in patients with pulmonary embolism: the link between D-Dimer level and thrombus volume", DOI: 10.1590/1806-9282.67.02.20200539, published in the Rev Assoc Med Bras. 2021;67(2):218-223.

Page 219, Methods, Study population, second paragraph:

Where it reads:
Patients between 18–65 years of age with optimum CTPA image quality and breathing, patients clinically and radiologically diagnosed with PE, were enrolled in the study.

It should read:
Patients aged 18 and over with optimum CTPA image quality and breathing, patients clinically and radiologically diagnosed with PE, were enrolled in the study.