Quantitative Evaluation of the Attenuation Value of Pulmonary Thrombus on Unenhanced Computed Tomography

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Objective: To identify pulmonary thromboembolism (PTE) using the thrombus attenuation value on unenhanced computed tomography (CT).


Method: Patients who underwent both unenhanced and enhanced CT for suspected PTE were enrolled. Patients with a hyperdense lumen on unenhanced CT and thrombi in the peripheral pulmonary artery (PA) were excluded. Patients were classified into two groups: thrombi (thrombi detected in PA by enhanced CT) and non-thrombi (attenuations of the main PA evaluated as thrombi). Mean CT attenuation values of the thrombi, main PA, and pulmonary trunk (blood pool) were measured. The attenuation values of the thrombus (T) and the thrombus to blood-pool (T/P), thrombus to hemoglobin (T/Hb), and thrombus to hematocrit (T/Hi) ratios were evaluated. The cut-off attenuation value of the thrombus was calculated by a receiver operating characteristic curve and its accuracy in detecting PTE was determined.

Results: Of the 250 patients enrolled, 40 were included, of whom 24 had confirmed PTE. The mean T was 27.25 Hounsfield units (HU) and 36.66 HU ($p<0.001$), and the T/P ratio was 0.74 and 0.99 ($p=0.004$) in the PTE and non-PTE groups, respectively. The thrombus cut-off value for PTE diagnosis was 30.85 HU. The sensitivity and specificity were 79.9% and 87.5%.

Conclusions: Measuring and evaluating the attenuation value for the central PA and T/P ratio on unenhanced CT improves the diagnostic ability of central PTE in patients suspected to have PTE but cannot tolerate contrast medium.

Key words: attenuation value of thrombus, pulmonary thromboembolism, unenhanced computed tomography (CT)

Abbreviations: PTE, pulmonary thromboembolism; CT, computed tomography; PA, pulmonary artery; HU, Hounsfield unit; T, thrombus attenuation value; T/P, thrombus to blood pool; T/Hb, thrombus to hemoglobin; T/Hi, thrombus to hematocrit; ROI, region of interest; ROC, receiver operating characteristic; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DVT, deep venous thrombosis

Introduction
Pulmonary thromboembolism (PTE) is a life-threatening disease with a mortality rate of 11.9%. Approximately 350,000 cases of PTE and 85,000 PTE-related deaths occur each year in Japan. The gold standard for definitive diagnosis of PTE is enhanced computed tomography (CT). However, the use of contrast media may be a concern for
certain patients, such as those with allergies to contrast media, patients medicated with biguanides, or those suffering from renal dysfunction. For these patients, detection of pulmonary thrombi on unenhanced CT could be useful for diagnosis and initiation of therapy for PTE.

High-density regions on unenhanced CT scans, or the hyperdense lumen sign, are known indicators of recent PTE. Current reports have shown that the CT attenuation value of the hyperdense lumen sign is 50-80 Hounsfield units (HU)\(^6\). However, the attenuation of the clots gradually decreases with time and becomes equal to or less than that of the blood pool. Therefore, pulmonary thrombi are rarely detected on unenhanced CT with the exception of the hyperdense lumen sign. We need to find other methods to detect PTE on unenhanced CT and there are no studies that measure the CT attenuation value of thrombi.

The purpose of this study was to examine the usefulness of the thrombus attenuation value on unenhanced CT for the diagnosis of PTE. We also assessed the cut-off CT values for PTE diagnosis using unenhanced CT in patients with PTE. This is the first study that quantitatively evaluated the CT attenuation value of thrombi.

**Materials and methods**

This study reviewed outpatients who presented with dyspnea, chest pain, syncope, and dizziness, showed low saturated oxygen in arterial blood and right heart load, and underwent enhanced CT at Showa General Hospital from January 2015 to March 2020.

All studies were performed using the GE\(^{8}\) light-speed VCT 64 detector (GE Healthcare, Hino, Japan) or the Canon Aquilion\(^9\) One 320 (Canon, Ota city, Tokyo, Japan) detector. The parameters were varied among the unenhanced and enhanced CT examinations, with slice thickness ranging from 3 mm to 5 mm at axial, coronal, and sagittal views. Patients were administered intravenous injections of 2 ml/kg non-ionic contrast medium (Iopromide: Iopromide Injection FTP\(^8\) 300 mgI/ml, FujiPharma, Toyama, Japan) at a rate of 3 ml/s. Scans were obtained 30 seconds after injection.

CT images were evaluated on a picture archiving and communications system workstation. Based on the enhanced CT images, patients were divided into the PTE group (thrombi were detected) (Figure 1A) or the non-PTE group (thrombi were not detected). Patients who underwent both enhanced and unenhanced CT were included. The central type of PTE was defined as a filling defect in the pulmonary trunk or in the main, lobar, and segmental pulmonary arteries (PAs). We excluded peripheral PTE filling defects in the subsegmental and more peripheral arteries. Patients who showed a hyperdense lumen sign on unenhanced CT were also excluded. The hyperdense lumen sign is a clot with hyperdensity in the PA on unenhanced CT (Figure 1B). In the central PTE group, patients who met the inclusion criteria were labeled as the thrombi group. Patients who met the inclusion

![Figure 1 A: Thrombi (arrow) in pulmonary artery on enhanced computed tomography. B: Hyperdense lumen sign (arrow): the same position of thrombi in Figure 1A.](image-url)
criteria in the non-PTE group were labeled as the non-thrombi group. CT attenuation values were then measured on unenhanced CT images. In the thrombi group, attenuation values were measured in relation to the thrombus after referring to its position in the enhanced CT image. The attenuation values of the pulmonary trunk were also measured after confirming that there was no thrombus on the enhanced CT image. In the non-thrombi group, the attenuation value of the PA was evaluated and compared to the attenuation value of the thrombi in the thrombi group. The attenuation value of the pulmonary trunk was also evaluated. These measurements were performed by placing the region of interest (ROI) in the scans, after which the computer automatically calculated the average attenuation values (in HU) for the selected foci (Figure 2A, 2B and 3). Each ROI was about 4-6 mm in diameter with an area of 12-28 mm², which was the maximum diameter possible without exceeding the diameter of the segmental PA. Although no specific window setting was used consistently in this study, results were best seen with narrow window settings (window width=330 HU, window level=30 HU). To reduce bias without affecting the partial volume effect, 3-5 ROIs were placed for each image.

Medical records were reviewed to assess the baseline characteristics of patients, including the presenting signs and symptoms, clinical diagnosis, indications for the procedure, and laboratory workups. The mean (± standard deviation [SD]) attenuation values (in HU) of the thrombus and main PA were compared. The thrombus attenuation value on unenhanced CT is related to the

Figure 2 Placing the region of interest (ROI) (●) on unenhanced computed tomography (CT) in the thrombi group. ROIs were placed on the thrombus (A) after referring to its position in the enhanced CT image (B).

Figure 3 Placing the region of interest (ROI) (●) on unenhanced computed tomography (CT) in the non-thrombi group. ROIs were placed on the pulmonary trunk and the left and right main pulmonary arteries.
patient's hematocrit (Ht) and hemoglobin (Hb) levels. Therefore, we also assessed the ratio of the attenuation value of thrombus (T) to Hb (T/Hb ratio), Ht (T/Ht ratio), and PA (T/P ratio). Receiver operating characteristic (ROC) analysis was performed to set the threshold of the diagnostic performance of unenhanced CT in detecting PTE. Sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively), and positive and negative likelihood ratios (PLR and NLR, respectively) as well as their 95% confidence intervals (CIs) for the diagnosis of PTE were calculated for each unenhanced CT finding. Continuous variables were tested by t-test or Mann–Whitney U test, discontinuous variables were tested by Fisher's exact test, and p-values <0.05 were considered significant. All statistical analyses were performed using EZR® (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

This study protocol was approved by the ethics committee of Showa General Hospital (approval number REC-240m). All patients provided written informed consent.

Results

A total of 260 patients were enrolled in the study; 200 were diagnosed with PTE and 60 were not, confirmed based on enhanced CT examination. Of the 200 patients with PTE, 151 did not undergo unenhanced CT examination and were excluded. Among the 49 patients with PTE who underwent both enhanced and unenhanced CT, 33 were of the central type, of whom 9 showed a hyperdense lumen sign and were also excluded. From the 60 patients in the non-PTE group, 17 underwent both enhanced and unenhanced CT, of whom 1 showed a hyperdense lumen sign and was excluded. After applying the exclusion criteria, a total of 40 patients were included in the analyses. Twenty-four of these patients had an acute central PTE (thrombi group), and sixteen had no thrombi in the PA (non-thrombi group) (Figure 4). There was no significant difference in age, renal function, or Hb values at the time of imaging between the two groups. D-dimer, fibrin, and fibrinogen degenera-

![Figure 4 Patient enrollment protocol](image-url)
tive product (FDP) were significantly higher in the thrombi group than in the non-thrombi group (Table 1).

The mean attenuation values of pulmonary blood pools in the thrombi and non-thrombi groups were 40.01±12.19 HU and 38.07±9.37 HU, respectively (p=0.594). The mean attenuation values of thrombi in the thrombi group and main PA in the non-thrombi group were 27.25±7.94 HU and 36.66±6.10 HU, respectively (p<0.001). The T/Hb ratio, T/Ht ratio, and T/P ratio in the PTE group were significantly lower than those in the non-thrombi group (Table 2). There was no significant difference in the attenuation values between the two CT devices.

The performance of unenhanced CT for PTE diagnosis is shown in Table 3. According to the ROC curve (Figure 5), a thrombus cut-off value of 30.85 HU and a T/P ratio cut-off value of 0.835 were associated with moderately accurate diagnosis of PTE (area under the curve=83.3 and 77.5, respectively). The thrombus sensitivity, specificity, PPV, NPV, and PLR were 79.2%, 87.5%, 90.5%, 73.7%, and 6.33, respectively (Table 3). The T/P

Table 1 Baseline characteristics of patients and initial testing results

<table>
<thead>
<tr>
<th>Factor</th>
<th>Thrombi (n=24)</th>
<th>Non-thrombi (n=16)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (f/m)</td>
<td>10/14</td>
<td>7/9</td>
<td>1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.08 (12.74)</td>
<td>71.88 (12.67)</td>
<td>0.167</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>20.64 (13.78)</td>
<td>16.27 (4.20)</td>
<td>0.288</td>
</tr>
<tr>
<td>Cre (mg/dl)</td>
<td>0.85 (0.29)</td>
<td>1.07 (0.76)</td>
<td>0.699</td>
</tr>
<tr>
<td>D-dimer (mg/dl)</td>
<td>22.95 (27.91)</td>
<td>1.17 (1.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FDP (mg/dl)</td>
<td>48.51 (65.95)</td>
<td>4.70 (3.25)</td>
<td>0.030</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>12.55 (2.72)</td>
<td>13.59 (2.68)</td>
<td>0.053</td>
</tr>
<tr>
<td>Ht (%)</td>
<td>38.53 (8.06)</td>
<td>41.42 (7.61)</td>
<td>0.065</td>
</tr>
<tr>
<td>Plt (10^4/µl)</td>
<td>24.73 (16.7)</td>
<td>19.77 (12.8)</td>
<td>0.288</td>
</tr>
</tbody>
</table>

Values are mean (± standard deviation).

BUN: blood urea nitrogen; CRE: creatinine; FDP: fibrinogen degenerative product; Hb: hemoglobin; Ht: hematocrit; Plt: platelet.

Table 2 Attenuation values in the pulmonary thrombus and pulmonary blood pool

<table>
<thead>
<tr>
<th></th>
<th>Thrombi (n=24)</th>
<th>Non-thrombi (n=16)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (HU)</td>
<td>40.01 (12.19)</td>
<td>38.07 (9.37)</td>
<td>0.594</td>
</tr>
<tr>
<td>T (HU)</td>
<td>27.25 (7.94)</td>
<td>36.66 (6.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T/Hb</td>
<td>2.29 (1.13)</td>
<td>2.76 (0.44)</td>
<td>0.015</td>
</tr>
<tr>
<td>T/Ht</td>
<td>0.74 (0.36)</td>
<td>0.90 (0.12)</td>
<td>0.012</td>
</tr>
<tr>
<td>T/P</td>
<td>0.74 (0.27)</td>
<td>0.99 (0.13)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Values are mean (± standard deviation); HU: Hounsfield unit; P: pulmonary blood pool (pulmonary trunk); T: thrombus; 1, thrombus; 2, main pulmonary artery; Hb: hemoglobin; Ht: hematocrit.

Figure 5 Receiver operating characteristic (ROC) curve of thrombus and the thrombus/pulmonary blood pool ratio. Solid line indicates the ROC of computed tomography (CT) attenuation values of thrombus. The cut-off values are 30.85 Hounsfield units (HU) for thrombus, 0.875 HU for specificity, and 0.792 for sensitivity. Dotted line indicates the ROC of the thrombus/pulmonary blood pool ratio. The cut-off values are 0.835 for the thrombus/pulmonary blood pool ratio, 0.875 for specificity, and 0.667 for sensitivity.
Table 3  Cut-off computed tomography values and the accuracy of unenhanced chest computed tomography for detecting pulmonary thromboembolism

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>PLR</th>
<th>NLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>T≤30.85</td>
<td>79.2 (57.8,92.9)</td>
<td>87.5 (61.7,98.4)</td>
<td>83.3 (69.4,97.3)</td>
<td>90.5 (69.9,98.6)</td>
<td>73.7 (48.9,90.9)</td>
<td>6.3 (1.7,21.3)</td>
<td>0.2 (0.1,0.5)</td>
</tr>
<tr>
<td>T/Hb≤2.53</td>
<td>62.5 (40.6,81.2)</td>
<td>87.5 (61.7,98.4)</td>
<td>72.9 (56.5,89.3)</td>
<td>88.2 (63.6,98.5)</td>
<td>60.9 (38.5,88.3)</td>
<td>5.0 (1.3,19.0)</td>
<td>0.4 (0.2,0.7)</td>
</tr>
<tr>
<td>T/Ht≤0.83</td>
<td>62.5 (40.6,81.2)</td>
<td>87.5 (61.7,98.4)</td>
<td>72.9 (56.5,89.3)</td>
<td>88.2 (63.6,98.5)</td>
<td>60.9 (38.5,88.3)</td>
<td>5.0 (1.3,19.0)</td>
<td>0.4 (0.2,0.7)</td>
</tr>
<tr>
<td>T/P≤0.835</td>
<td>66.7 (44.7,84.0)</td>
<td>87.5 (61.7,98.4)</td>
<td>77.5 (62.7,92.2)</td>
<td>88.9 (65.3,98.6)</td>
<td>63.6 (40.7,82.8)</td>
<td>5.3 (1.4,20.1)</td>
<td>0.4 (0.2,0.7)</td>
</tr>
</tbody>
</table>

Values (95% confidence interval); P: computed tomography value for pulmonary artery blood pool (Hounsfield unit); T: computed tomography value for thrombus (Hounsfield unit); Hb: hemoglobin (g/dL); Ht: hematocrit (%); AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative likelihood ratio

Discussion

A thrombus in the pulmonary trunk or main PA is a life-threatening disease, and a prompt diagnosis is critical for a favorable outcome. Recent reports have shown that several signs of PTE have been observed via unenhanced CT, including a hyperdense lumen sign, PA dilatation, and wedge-shaped consolidation. Among these signs, the hyperdense lumen has a high diagnostic performance, but it only occurs in 50-70% of cases. In our study, only 9 of 49 patients (18%) showed a hyperdense lumen sign.

To date, no study has evaluated the CT attenuation value for patients with PTE using quantitative indicators on unenhanced CT images. This study aimed to evaluate the thrombus attenuation cut-off value for PTE diagnosis. The thrombus attenuation value was lower in the thrombi group than in the non-thrombi group. Additionally, the attenuation value of thrombus in the thrombi group was lower than that in the blood pool. The thrombus cut-off value of 30.85 HU calculated from the ROC curve showed good accuracy. Our results indicate potential benefits of using measurements of thrombus attenuation values on unenhanced CT to detect PTE. This study is the first to evaluate the usefulness and reliability of thrombus attenuation value on unenhanced CT in patients with PTE.

The blood pool attenuation value is mainly determined by the protein content of red blood cells and it increases linearly with Ht. The blood pool attenuation value is 20-60 HU, whereas the density of the thrombus is determined by the concentration of red blood cells and fibrin. From a pathologic point of view, the different densities of the thrombus can be explained by the processes undergone by the clot itself while lodged within the PA system. As a thrombus retracts, its water content decreases, which concentrates the hemoglobin and raises the CT attenuation value of thrombi to 50-80 HU. The attenuation of clots decreases gradually to the same as or lower than that of the blood. Acute thrombi—clinically judged to be <8 days old—have an average attenuation value of 66 HU, whereas those older than 8 days have a lower value. In PTE, thrombi are primarily caused by deep venous thrombosis (DVT). As DVT has varied symptoms (and can be asymptomatic in some cases), it is difficult to accurately determine when a DVT had formed. This study included emergency outpatients, but it is possible that several days had passed since the clot had formed. This is probably why the CT images showed a hypoattenuation clot.

The attenuation value of thrombosis is related to the age of clots and Hb and Ht levels. To eliminate any bias because of the Hb and Ht factors, we also evaluated the T/Hb, T/Ht, and T/P ratios. Our hypothesis is that T/Hb, T/Ht and T/P ratios are more useful than the attenuation value of T alone. There were significant differences for T/Hb, T/Ht and T/P ratios, but sensitivity, PPV, and PLR of the T/Hb and T/Ht ratios were lower than those of the thrombus. The attenuation of a blood-pool CT value becomes 1.7-2.0 HU lower when the Hb drops 1 g/dL. This was a very small change, and so there were no noticeable changes in the T/Hb and T/Ht ratios. Sun et al. stratified Hb levels into 4 classes and attempted to determine the effect of the Hb value on the accuracy of PTE identification. However, patients with anemia were not more likely to be diagnosed as truly positive for PTE.

One non-PTE patient showed a hyperdense
lumen sign in our study. The descending aorta showed several calcifications in her unenhanced CT. This may occur with atherosclerotic disease of the PA. We misunderstood a calcification for a hyperdense lumen sign.

In conclusion, the T/Hb ratio and T/Ht ratio were not useful for the diagnosis of PTE, but the thrombus attenuation value and the T/P ratio were useful. Patients in whom PTE is clinically suspected, attenuation values should be measured at multiple points in the main and lobar PAs and a few points in the pulmonary trunk. PTE is suspected when the attenuation value is below 30.85 HU or when the T/P ratio is below 0.835, and thus an enhanced CT can confirm the presence of PTE.

There are several limitations to this study. This study was retrospective in nature. The thrombus attenuation values in unenhanced CT were measured after the thrombi were detected by enhanced CT and cut-off values were not considered in a healthy population. In future studies, we will assess whether PTE can be found via unenhanced CT with a fixed window width of 45 and window level of 70, which was obtained from this present study. The minimum and maximum pulmonary blood attenuation values were 20.15 HU and 71.55 HU. The minimum and maximum thrombus attenuation values were 11.75 HU and 44.75 HU. In addition, this was a single-center study with a small sample size, and a larger sample size could improve the accuracy of our results.

Our results show that the probability of PTE was extremely high in patients who had a central PA attenuation value below 30.85 HU and a T/P ratio below 0.835. This study suggests that assessing the attenuation value for the central PA and T/P ratio on unenhanced CT improves the diagnostic ability of central PTE in patients with suspected to have PTE but who cannot tolerate contrast medium, and whose unenhanced CT does not show hyperdense lumen sign, PA dilatation and wedge-shaped consolidation.

Acknowledgments

We are grateful to the radiation technologist for help with data collection.

Funding

The authors received no financial support for the research.

Authors' contributions

MI conceived and designed the study, collected and analyzed the data, drafted the manuscript, and revised it critically for important intellectual content. TN interpreted the data and drafted and revised the manuscript. YU interpreted the CT data. MS, HI, and YO revised the manuscript critically and provided important intellectual content. All authors have read and approved the final version of manuscript.

Conflicting interest statement

The authors declare no conflicting interests.

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