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Clinical characteristics for distinguishing between acute cardiogenic pulmonary edema and community-acquired pneumonia in elderly patients: a prospective observational study

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Patient consent for publication: Written informed consent was obtained from the participants.

Informed consent: Written informed consent was obtained from the participant

Abstract

Heart failure and pneumonia are highly prevalent in elderly patients. We conducted a study to evaluate the differences in the patterns of symptoms, laboratory findings, and computed tomography (CT) results in elderly patients with acute cardiogenic pulmonary edema (ACPE) and community-acquired pneumonia (CAP). From January 1, 2015 to December 31, 2017, we studied 140 patients aged >75 years who were diagnosed with ACPE and CAP. Symptoms, laboratory findings, mean ostial pulmonary vein (PV) diameter and patterns on CT images were assessed. The primary measures of diagnostic accuracy were assessed using the positive likelihood ratio (LR+). The cutoff value of ostial PVs for differentiating patients with ACPE from CAP was evaluated using the receiver operating characteristic (ROC) analysis. Ninety-three patients with ACPE, 36 with CAP, and 11 with complicated ACPE/CAP were included. In patients with ACPE, edema (LR+ 5.4) was a moderate factor for rule-in, and a high brain natriuretic peptide level (LR+ 4.2) was weak. In patients with CAP, cough (LR+ 5.7) and leukocytosis (LR+ 5.2) were moderate factors for rule-in, while fever (LR+ 3.8) and a high C-reactive protein level (LR+ 4.8) were weak factors. The mean diameter of ostial PVs in patients with ACPE was significantly larger than that of patients with CAP (15.8±1.8 mm *vs* 9.6±1.5 mm, $p<0.01$). ROC analysis revealed that an ostial PV diameter cutoff of 12.5 mm was strong evidence for distinguishing ACPE from CAP with an area under the ROC curve of 0.99 and LR+ 36.0. In conclusion, as ACPE and CAP have similar symptoms and laboratory findings, dilated ostial PVs were useful in characterizing CT images to distinguish ACPE from CAP.

Key words: acute cardiogenic pulmonary edema; ostial pulmonary veins; elderly; pneumonia.

Introduction

Heart failure (HF) and community-acquired pneumonia (CAP) are two major public health problems associated with high morbidity and mortality in the elderly population. The prevalence and incidence of HF and CAP progressively increase with age. Hospitalizations for acute HF and CAP are increasingly common among elderly patients older than 65 years of age [1], with annual hospitalization rates of 7-61 per 1,000 and 21.5 per 1,000, respectively [2]. Approximately 20% of the patients with HF have concomitant CAP [3]. Acute respiratory tract infection is the main precipitating event for 3-16% of patients hospitalized with HF; conversely, HF is a risk factor for CAP [4]. Unfortunately, the symptoms and signs of CAP are not specific, and even with chest radiograph features compatible with acute pulmonary inflammation, 5-17% of patients admitted to the hospital with CAP may have a non-infectious condition mimicking CAP [5,6].

A patient with acute cardiogenic pulmonary edema (ACPE) due to HF exacerbations can present similarly to a patient with CAP. Patients with ACPE commonly present with cough, shortness of breath, fatigue, and/or peripheral edema. Clinical presentation, routine laboratory test results, and chest radiography findings seem to have limited value in differentiating ACPE from CAP [7]. Radiographic signs of ACPE include left atrial enlargement, pulmonary venous engorgement, peribronchial patterns, and air bronchograms. A deep knowledge of the chest computed tomography (CT) signs of ACPE is crucial when other similar pulmonary conditions may occasionally be in the differential diagnosis [8,9]. No distinction can be made between patients with pulmonary edema and those with pneumonia, as data on CT images are rare and invalidated. Gao *et al*. investigated that patients with ACPE demonstrated significant dilation of the pulmonary veins (PVs) on CT images compared to healthy patients [10]. However, it is unclear whether the dilation of PVs is useful for distinguishing ACPE from CAP.

In this study, we investigated the clinical presentations and laboratory findings to find useful diagnostic findings in ACPE and CAP. We also assessed the CT image pattern and the diameter of PVs and whether ACPE and CAP can be distinguished from them.

Materials and Methods

Study design and patients

Two hundred forty-seven and 618 patients were admitted to our hospital with ACPE and CAP between January 2015 and December 2017 (Figure 1). They were diagnosed in the emergency

unit with ACPE due to HF, which is defined as the sudden or gradual onset of the signs of HF requiring unplanned hospitalization, and CAP [8,11]. All patients were hospitalized within 24 hours and underwent chest CT and measurement of serum brain natriuretic peptide (BNP) levels (Table 1). Finally, patients who showed findings of edema in the lung interstitium and/or alveoli caused by cardiac dysfunction were diagnosed with ACPE. Patients with cardiogenic shock, pneumonia, non-cardiogenic pulmonary edema, or acute coronary heart disease were excluded. Patients with CAP admitted concomitantly were also enrolled. Diagnosis of CAP is suggested based on a history of cough, dyspnea, pleuritic pain, or acute functional or cognitive decline, with abnormal inflammatory markers (e.g., white blood cells and C-reactive protein [CRP]) and abnormal findings on lung chest radiography [12-14]. Conditions that mimic CAP were excluded based on whether the patient's condition failed to improve with antibiotic management.

Measurement of BNP levels

Blood samples were collected for biochemical and cardiac enzyme analyses. BNP is a useful biomarker for ACPE assessment, and its level was measured within 24 h of onset.

Imaging technique

Chest CT scans were obtained using an Aquilion CXL 64 scanner (Toshiba, Tokyo, Japan). Scanning parameters were 120 kVp and 50–190 mA. The section thickness was 5.0–10.0 mm from the lung apex to the lung base. All images were reconstructed using high-spatial-frequency or bone algorithms and displayed with a lung window setting (window level: -700 to -800 HU; width: 1500 HU). Chest CT findings were independently evaluated by one radiologist and one pulmonologist who were unaware of the patient's clinical information.

The diameters of the four ostial pulmonary veins (PVs) were measured on CT images, and their mean values were assessed as the diameter of the ostial PVs. We measured each ostial PV diameter at the level of the cross point of the ostial PV axis and the gate of the left atrium (Figure 2A). The patterns, extent, and distribution of the lung lesions were analyzed. The different patterns were classified as consolidation, ground-glass opacity, interlobular septal thickening, bronchovascular bundle thickening, intralobular interstitial thickening, and nodules. The presence of contralateral lung involvement and pleural effusion were also assessed.

Statistical analyses

Continuous variables are presented as mean ± SD. The distribution of continuous data was evaluated by Shapiro-Wilk test graphs (histograms and Q-Q plots), and they showed a non-normal distribution for the mean values of ostial PV ($p<0.05$). The Kruskal-Wallis with the Steel-Dwass test is utilized for all statistical analyses of continuous data [15]. Categorical data are presented as values and percentages. Differences in categorical variables between the subgroups were statistically tested using the Fisher's exact test, followed by the Benjamini-Hochberg procedure for multiple comparison correction [16]. The cutoff value of the ostial PV diameter for differentiating patients with ACPE from control patients was evaluated by receiver operating characteristic (ROC) analysis, and its sensitivity, specificity, and accuracy were calculated. All statistical analyses were performed using the R Project for Statistical Computing, version 3.2.5 (Vienna, Austria). A p-value <0.05 was considered statistically significant.

The plot of specific ROC curves was used to evaluate the best cutoff point that could predict the probability of ACPE and CAP. The cutoff point was derived from the ROC curves based on the maximal Youden index, which was calculated as sensitivity+specificity−1, to reflect the maximal correct classification accuracy. Then, the accuracy of symptoms and laboratory findings in predicting ACPE and CAP was calculated in terms of sensitivity and specificity for this cutoff point. An area under the curve (AUC) >0.9 was defined as high accuracy, between 0.9 and 0.7 as moderate accuracy, and <0.7 as low accuracy [17]. The positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were the primary measures of diagnostic accuracy. An LR+ >10, indicating an estimated shift in probability of at least 45%, is very strong evidence to rule in disease, whereas between 5 and 10 is moderate (estimated shift of at least 30%) and between 2 and 5 is weak (estimated shift 15%) [18,19]. Reliability was calculated as the intra-class correlation coefficient (ICC), with a value >0.75 considered as a good correlation.

Results

Patient characteristics

Among the 247 and 618 patients admitted to our hospital with ACPE and CAP between January 2015 and December 2017, we excluded 143 and 582 patients with ACPE and CAP, respectively. In total, 140 patients, 93 with ACPE, 11 with ACPE/CAP, and 36 with CAP met the inclusion and exclusion criteria in this prospective observational study (Figure 1). The underlying causes of ACPE and ACPE/CAP included chronic atrial fibrillation (n=41), hypertensive HF (n=36), cardiomyopathy (n=15), and valvular heart disease (n=13). Table 1 shows the baseline clinical

characteristics of the three groups. Patients' mean age was no significant difference between the groups. Patients with ACPE predominantly had etiologies of chronic AF compared to those with CAP (55.8% *versus* 34.7%) and dilated cardiomegaly (26.5% vs. 4.7%). Analysis of the differences revealed that patients with CAP significantly showed a higher prevalence of fever, cough, appetite loss and higher inflammatory signs than patients with ACPE ($p<0.01$). In contrast, patients with ACPE significantly demonstrated a higher prevalence of edema and mean BNP level ($p<0.01$).

Accuracy of diagnosing ACPE and CAP based on symptoms and laboratory findings

In the analysis of the symptoms and clinical findings distinguishing ACPE from CAP (Table 2), edema, dyspnea and a high BNP level had evidence to rule in ACPE. The best variable for ruling out ACPE was the BNP level. In CAP (Table 3), cough, fever and appetite loss had evidence to rule in.

Diameter of ostial PVs on CT

We assessed ostial PV diameter in patients with ACPE, CAP, and ACPE/CAP. The intra-examiner reproducibility test showed that the ICC was 0.89 for the diameter of ostial PVs. The diameter of ostial PVs was calculated as the mean of the measurable ostial PVs. The mean diameter of ostial PVs in patients with ACPE was significantly larger than that of patients with CAP (15.8±1.8 mm vs. 9.6±1.5 mm, $p<0.01$) (Table 4). ROC analysis showed that an ostial PV cutoff ≧12.5 mm had a sensitivity of 100%, a specificity of 99.8%, and an accuracy of 98.8% in diagnosing ACPE, with an area under the ROC curve of 0.99 (Figure 4).

CT findings of ACPE

Table 4 shows CT findings of patients with each group and Figure 3 shows typical patterns of CT images. Bilateral pleural effusion, ground-glass opacities, interlobular septal thickening and peri-bronchovascular thickening were significantly observed in ACPE compared with CAP ($p<0.01$). In contrast, consolidation was significantly observed in CAP ($p<0.01$).

Discussion

Our results show that dilated ostial PVs were more in ACPE, and it is useful for distinguishing ACPE from CAP in elderly patients. Edema, high BNP level and bilateral pleural effusion were

helpfully ruled in ACPE, whereas cough, appetite loss and inflammatory marker level were helpfully ruled in CAP.

First, we determined the differences in the symptoms between ACPE and CAP. The classic presentation of CAP is cough, shortness of breath, and fever. The most common signs of pneumonia include cough (79-91%), fever (up to 75%), increased sputum (up to 65%), pleuritic chest pain (up to 50%), and dyspnea (approximately 70%) [20]. However, elderly or debilitated patients can present with non-specific complaints [21,22]. Our result for high fever (36.1%) was consistent with that of a previous report that reported a low prevalence of high fever in elderly patients with CAP (33-60%) [23]. BNP was reported to be more likely to be elevated in chronic HF exacerbations, although sepsis from pneumonia can also increase the BNP level [21]. Our results demonstrated that symptoms and laboratory findings showed weak evidence for ruling in ACPE or CAP. Therefore, conditions that mimic pneumonia are not even considered in patients with a classic presentation of pneumonia until the patient fails to improve with initial antibiotic management.

ACPE frequently presents as CAP [6]. In patients with areas of altered pulmonary perfusion due to bullae, chronic obstructive pulmonary disease, or valvular disease, pulmonary edema may appear as localized infiltrates on chest radiographs. An enlarged cardiac silhouette should raise the suspicion of cardiac disease. Primary cardiac disease with pulmonary edema may predispose patients to infectious pneumonia. Chest radiography findings in congestive HF may include prominent interstitial markings, cardiomegaly, and pleural effusions [24]. However, in an emergency setting, performing chest radiography while the patient is standing is not possible. Anteroposterior chest radiography performed in the supine position results in false magnification, which can exaggerate cardiomegaly [25].

ACPE is one of the most serious consequences of left ventricular cardiac failure. When the left ventricle fails or the mitral valve fails, left atrial pressure may increase substantially, followed by congestion of ostial PVs and increased pulmonary capillary pressure. This causes interstitial edema due to fluid movement from the blood vessels to the interstitial space, and when it progresses further, intra-alveolar edema occurs, resulting in ACPE [8]. From the mechanism of ACPE development, it seems that the PV diameter expands from an early stage at the onset of pulmonary edema; therefore, measurement of the PV diameter for ACPE evaluation will be useful. Our results are in accordance with those of Gao *et al*., demonstrated that patients with congestive HF had significant dilation of ostial PVs on CT [10]. In our study, a cutoff of 12.5 mm for ostial PVs was attributed to higher accuracy for diagnosing ACPE. Approximately 90%

of patients with ACPE had bilateral pleural effusion. Additionally, dilated ostial PVs showed strong evidence of ruling in ACPE.

On chest CT, signs of hydrostatic edema result from a combination of septal thickening and ground-glass opacities. The incidence and predominance of these signs are individually variable [24,26]. The most common CT findings in the parenchyma of patients with ACPE are ground-glass opacities (100%), interlobular septal thickening (100%), peri-broncho-vascular thickening (80%), mosaic pattern of attenuation (67%), and consolidation (33%). The prevalence of patterns on CT images was inconsistent with our results; however, the order of frequency was consistent with our results, such as interstitial edema followed by alveolar edema.

This study has several limitations. First, this was a single-center study with a small sample size, in which clinical efficacy was observed. Despite the small sample size, this study had a homogeneous group and eliminated assumption bias. Therefore, a large study without selection bias is required. Second, the CT images were assessed only once on admission. In acute HF, a time lag is often observed between the increased pulmonary capillary wedge pressure and the radiologic manifestation of pulmonary edema due to the slow movement of water through the widened capillary endothelial cell junctions [27]. Third, the dilation of ostial PVs is affected by cardiovascular diseases [28]. For example, patients with AF undergo structural changes due to organic remodeling of the left atrium, resulting in dilation of the PVs [28]. Fourth, although we evaluated only axial images, a multidirectional evaluation should be performed because the PV diameter is oval and deformed by heart movement [29]. Lastly, since the right PVs are larger than the left PVs, which are affected by surrounding structures, the results may vary depending on which PV is measured [29].

Conclusions

In conclusion, as ACPE and CAP have similar symptoms and laboratory findings, it can be difficult to diagnose only on physical examination and blood tests. An ostial PV cutoff ≧12.5 mm had a sensitivity of 100%, a specificity of 99.8%, so dilated ostial PVs is useful CT findings for distinguishing ACPE from CAP.

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Table 1. Characteristics of patients with ACPE, CAP, and ACPE/CAP. Continuous variables are presented as median (range), and categorical data are represented as value and percentage. The non-parametric Kruskal-Wallis was used to compare continuous variables between groups, and then the Steel-Dwass test was used as a post-hoc analysis. Differences in categorical variables between the subgroups were statistically tested using the Fisher exact test, followed by the Benjamini-Hochberg procedure for multiple comparison correction [20].

	Patients with ACPE	Patients with ACPE/CAP	Patients with CAP
n	93	11	36
Age, years	88.0 (75–100)	90 (81–97)	90 (75–97)
Female sex, %	57%	36%	42%
Symptom			
Body temperature, °C	36.6 (34.9–38.6)	37.3 (36.1–40.0)$^{\#}$	37.9 (35.8–40.1)*
Fever§, %	20.4%	63.6%*	66.7%*
High fever$^{\wedge}$, %	5.4%	18.2%*	36.1%*
SpO_2, %	90.4 (72.0–99.0)	88.0 (70.0–98.0)	93.0 (68.0–98.0)
SpO_2 <94%	61.3%	81.8%	58.3%
Dyspnea	65.6%	45.5%	13.9%*
Cough	5.4%	9.1%	16.7%*
Wheeze	1.1%‡	36.4%	2.8%‡
Edema	30.1%	9.1%	2.8%*
Appetite loss	5.4%	18.2%*	16.7%*
Altered mentation	0%	18.2%	5.6%
Bone fracture	0%	0%	8.3%
Laboratory findings			
WBC count, /μL	6,600 (2,800–16,300)	8,400 (2,600–24,210)	10,700 (2,800–19,700)*
CRP level, mg/mL	0.7 (0.02–21.72)	6.56 (0.39–29.31)*	11.4 (0.03–31.91)*
BNP level, pg/mL	663.5 (52.6–5,936.5)	406.8 (146.6–1,158.2)	134.6 (14.1–612.0)$^{*\circ}$

*p<0.01, $^{\#}$p<0.05 *vs* patients with ACPE; $^{\circ}$p<0.01 *vs* patients with ACPE/CAP; §fever was defined as an axillary temperature ≥37.2°C; $^{\wedge}$high fever was defined as an axillary temperature ≥38.0°C; ACPE, acute cardiogenic pulmonary edema; CAP, community-acquired pneumonia; SpO_2, oxygen saturation; WBC, white blood cell; CRP, C-reactive protein; BNP, brain natriuretic peptide.

Table 2. Diagnostic abilities of the symptoms and laboratory findings for acute cardiogenic pulmonary edema (ACPE).

	AUC	95% CI	Sensitivity	Specificity	LR+	LR-
Symptom						
Dyspnea	0.73	0.64–0.81	0.68	0.78	3.0	0.41
Wheeze	0.52	0.47–0.57	0.10	0.94	1.7	0.96
Edema	0.62	0.56–0.68	0.30	0.94	5.4	0.74
Laboratory finding						
BNP level ≥250 pg/mL	0.89	0.85–0.95	0.81	0.81	4.2	0.24
CT finding						
Bilateral pleural effusion	0.73	0.65–0.82	0.83	0.64	2.3	0.27
Ostial PVs ≥12.5 mm	0.99	0.97–1.00	1.00	0.97	36	0

Positive likelihood ratio (LR+) = sensitivity/(1-specificity); negative likelihood ratio (LR-) = (1-sensitivity)/specificity. AUC, area under the curve; CI, confidence interval; BNP, brain natriuretic peptide; CT, computed tomography; PV, pulmonary vein.

Table 3. Diagnostic abilities of the symptoms and clinical findings for community-acquired pneumonia (CAP).

Symptom	AUC	95% CI	Sensitivity	Specificity	LR+	LR-
Cough						
Appetite loss	0.63	0.55–0.71	0.31	0.95	5.7	0.73
Confusion of new onset	0.58	0.51–0.65	0.22	0.94	3.4	0.83
Body temperature ≥37.2°C	0.53	0.49–0.57	0.05	0.94	1.0	0.99
Desaturation	0.80	0.71–0.89	0.61	0.84	3.8	0.46
Laboratory finding	0.51	0.40–0.62	0.67	0.37	1.1	0.97
WBC count ≥10,000/μL	0.80	0.71–0.90	0.61	0.88	5.2	0.46
CRP level ≥5.5 mg/dL	0.83	0.74–0.92	0.72	0.85	4.8	0.33

Positive likelihood ratio (LR+) = sensitivity/(1-specificity); negative likelihood ratio (LR-) = (1-sensitivity)/specificity. AUC, area under the curve; CI, confidence interval; WBC, white blood cell; CRP, C-reactive protein.

Table 4. Computed tomography findings of patients with ACPE, CAP, and ACPE/CAP. Continuous variables are presented as median (range), and categorical data are represented as value and percentage. The non-parametric Kruskal-Wallis was used to compare continuous variables between groups, and then the Steel-Dwass test was used as a *post-hoc* analysis. Differences in categorical variables between the subgroups were statistically tested using the Fisher exact test, followed by the Benjamini-Hochberg procedure for multiple comparison correction [20].

	Patients with ACPE	Patients with ACPE/CAP	Patients with CAP
n	93	11	36
Ground-glass opacities	49.5%	27.3%	2.8%*
Interlobular septal thickening	43.0%°	27.3%	0%*
Bilateral pleural effusion	86.0%	45.5%	30.0%*
Unilateral pleural effusion	5.4%	18.2%	22.2%#
Peri-bronchovascular thickening	25.8%	0%	0%*
Mosaic pattern of attenuation	10%	0%	0%
Consolidations	8.6%	72.7%*	75.0%*
Diameter of PVs, mm	15.8 (12.8–22.2)	12.8 (8.1–15.2)*	9.6 (6.3–15.2)*

*p<0.01, #P<0.05 *vs* patients with ACPE; °p<0.01 *vs* patients with ACPE/CAP. ACPE, acute cardiogenic pulmonary edema; CAP, community-acquired pneumonia; PV, pulmonary vein.

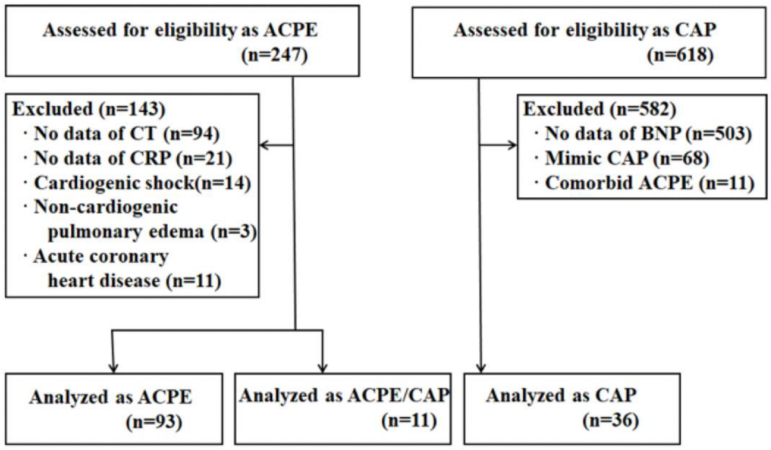

Figure 1. Consort diagram of patient selection.

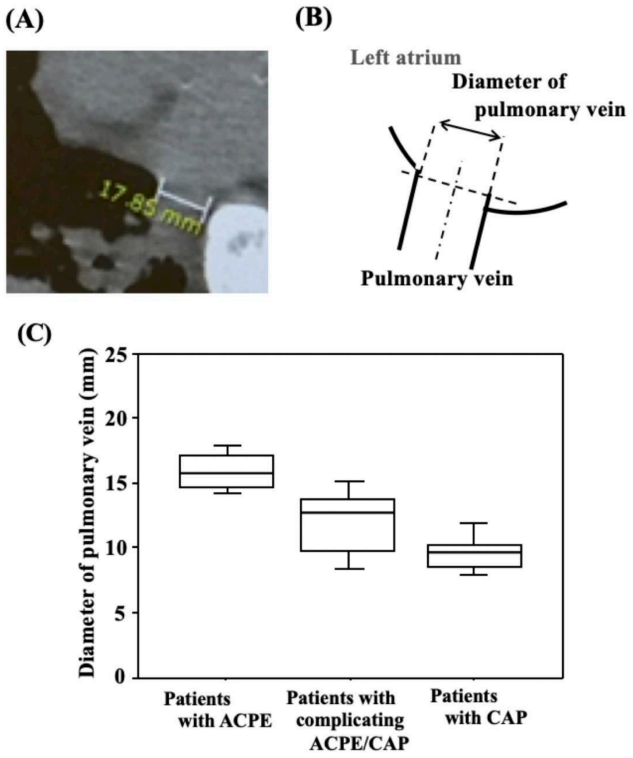

Figure 2. A) The representative pattern of dilated ostial pulmonary veins (PVs) in patients with acute cardiogenic pulmonary edema (ACPE). B) Method of measuring ostial PVs; the diameters of four ostial pulmonary veins (PVs) are measured on CT images at the level of cross point of the ostial PV axis and gate of the left atrium. C) Comparison of the diameter of ostial PVs between the three groups: patients with ACPE (n=93), community-acquired pneumonia (CAP) (n=36), and ACPE/CAP (n=11). CT, computed tomography; ACPE, acute cardiogenic pulmonary edema; CAP, community-acquired pneumonia.

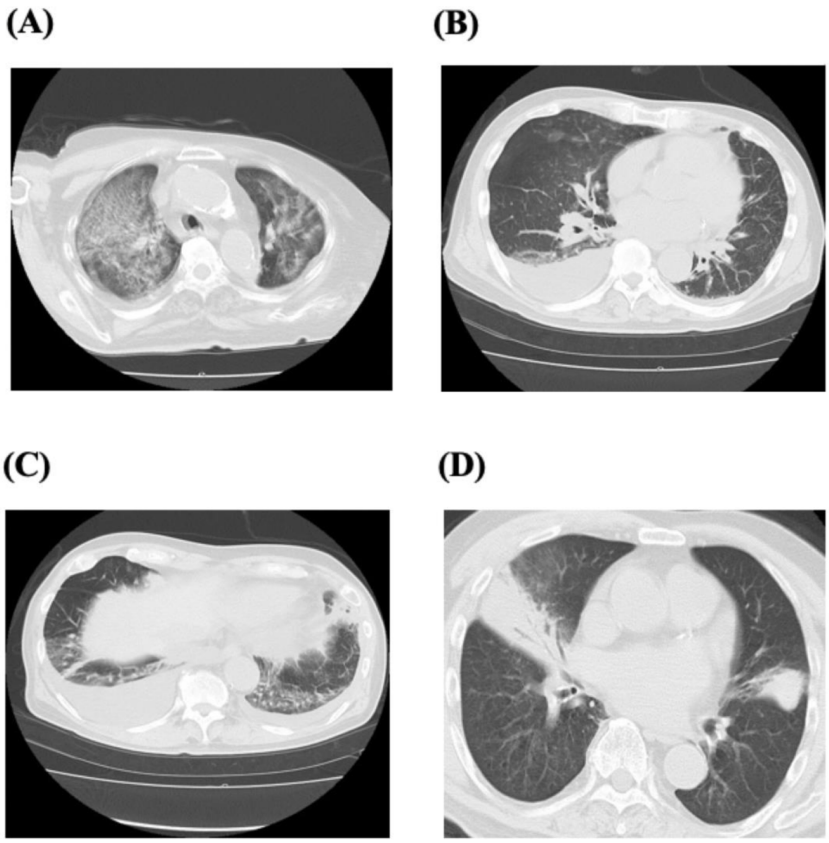

Figure 3. Representative computed tomography images of patients with acute cardiogenic pulmonary edema showing ground glass opacities (A), thickening of the interlobular septa and subpleural edema (B), peri bronchovascular interstitial thickening (C), and consolidation (D).

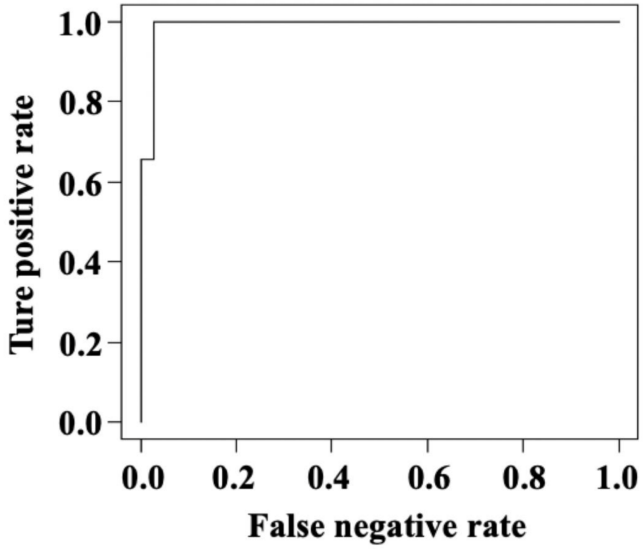

Figure 4. Receiver operating characteristic curves between patients with acute cardiogenic pulmonary edema (n=93) and patients with community-acquired pneumonia (n=11).