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N Piyavisetpat

K. Kittisatra

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CT features using in differentiating pleural exudates from transudates

Nitra Piyavisetpat*

Khanitha Kittisatra*

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Background : *Pleural effusion is one of the most frequent findings of thoracic abnormality, detected by computed tomography (CT). Differentiation between exudative from transudative effusions is crucial for diagnosis of various pathologies.*

Objective : *To determine the accuracy of computed tomography in enabling differentiation of pleural exudates from transudates.*

Setting : *King Chulalongkorn Memorial Hospital.*

Research design : *A retrospective study.*

Patients : *Patients who had pleural effusions and underwent CT of thorax and thoracentesis within 14 days of each other from March 2005 to August 2007 were recruited.*

Methods : *We analyzed 41 pleural effusions in 41 patients. Effusions were classified as transudates or exudates using laboratory markers based on Light's criteria. All CT scans were reviewed for the mean CT attenuation values and distribution of an effusion, the presence and appearance of pleural thickening, thickening and increased attenuation of extrapleural fat.*

*Department of Radiology, Faculty of Medicine, Chulalongkorn University

Results : *Thirty-four effusions were exudates, and 7 were transudates. The optimal threshold value was determined to be 11.75 HU for differentiation of pleural exudates. The mean attenuation value of exudates (14.8 ± 5.8 HU) was higher than transudates (10.7 ± 5.1 HU), but there was no detected significant difference (p = 0.09). Loculation of pleural effusion was found in 52.9% of exudates, with 53% sensitivity, 100 % specificity and 61% accuracy. Pleural thickenings were found in 61.8% of exudates and in 14.3% of transudates, with 62% sensitivity, 86% specificity and 66% accuracy. Extrapleural fat was thickened in 29.4% of exudates, and 64.7% of transudates. The attenuation of extrapleural fat was increased in 64.7% of exudates and 28.6% of transudates. None of transudates had loculated effusion, nodular pleural thickening nor thickening of extrapleural fat. The sensitivity, specificity and accuracy of extrapleural fat thickening were 29%, 100% and 41%; and of increased attenuation of extrapleural fat were 65%, 71% and 66%, respectively.*

Conclusion : *Loculation of pleural effusion, nodular pleural thickening and thickening of extrapleural fat at contrast-enhanced CT are highly suggestive of the presence of pleural exudates. CT attenuation values of exudates are higher than transudates, but there were no clinical value in differentiating exudates from transudates.*

Keywords : *Pleural effusion, transudate, exudate, computed tomography.*

Reprint request: Piyavisetpat N. Department of Radiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

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บทนำ : *น้ำในช่องเยื่อหุ้มปอดเป็นความผิดปกติที่พบได้บ่อยในการตรวจทรวงอกด้วยเครื่องเอกซเรย์คอมพิวเตอร์ การแยกระหว่างน้ำในช่องเยื่อหุ้มปอดชนิด exudates และชนิด transudates มีความสำคัญในการวินิจฉัยโรคต่าง ๆ*

วัตถุประสงค์ : *เพื่อศึกษาความแม่นยำในการใช้เอกซเรย์คอมพิวเตอร์ในการแยกระหว่างน้ำในช่องเยื่อหุ้มปอดชนิด exudates และชนิด transudates*

สถานที่ที่ทำการศึกษา : *โรงพยาบาลจุฬาลงกรณ์*

รูปแบบการวิจัย : *การศึกษาย้อนหลัง*

ผู้ป่วยที่ทำการศึกษา : *ผู้ป่วยที่มีน้ำในช่องเยื่อหุ้มปอด และได้รับการตรวจด้วยเอกซเรย์คอมพิวเตอร์ทรวงอก และการเจาะน้ำในช่องเยื่อหุ้มปอดในระยะเวลาห่างกันไม่เกิน 14 วัน ระหว่างมีนาคม 2548 ถึงสิงหาคม 2550*

วิธีการศึกษา : *ผู้วิจัยได้ทำการวิจัยน้ำในช่องเยื่อหุ้มปอดจากผู้ป่วย 41 รายที่ตรวจพบด้วยเครื่องเอกซเรย์คอมพิวเตอร์ โดยศึกษาค่าเฉลี่ยและการกระจายตัวของน้ำในช่องเยื่อหุ้มปอด การหนาตัวและลักษณะการหนาตัวของเยื่อหุ้มปอด การหนาตัวและลักษณะของ extrapleural fat ในการแยกระหว่างน้ำในช่องเยื่อหุ้มปอดชนิด exudates และ ชนิด transudates โดยใช้น้ำในช่องเยื่อหุ้มปอดที่ได้จากการเจาะและส่งตรวจในห้องปฏิบัติการโดยใช้ Light's criteria เป็นเกณฑ์มาตรฐานในการแยกระหว่างน้ำในช่องเยื่อหุ้มปอดชนิด exudates และ transudates*

ผลการศึกษา : *มีน้ำในช่องเยื่อหุ้มปอดชนิด exudates 34 ราย และชนิด transudates 7 ราย พบว่าค่าเฉลี่ยของน้ำในช่องเยื่อหุ้มปอดชนิด exudates (14.8 ± 5.8 HU) สูงกว่าชนิด transudates (10.7 ± 5.1 HU) แต่ไม่มีนัยสำคัญทางสถิติ ($p = 0.09$) การกระจายตัวของน้ำในช่องเยื่อหุ้มปอดแบบไม่อิสระพบในชนิด exudates ร้อยละ 52.9 โดยมีความไว ความไวจำเพาะ และความแม่นยำในการแยกระหว่างน้ำในช่องเยื่อหุ้มปอดชนิด exudates และ transudates ร้อยละ 53, 100 และ 61 ตามลำดับ การหนาตัวของ*

เยื่อหุ้มปอดพบในน้ำในช่องเยื่อหุ้มปอดชนิด exudates ร้อยละ 61.8 และในชนิด transudates ร้อยละ 14.3 โดยมีความไวร้อยละ 62 ความไวจำเพาะร้อยละ 86 และความแม่นยำร้อยละ 61 ในการแยกชนิดของน้ำในช่องเยื่อหุ้มปอด การหนาตัวของ extrapleural fat พบในชนิด exudates ร้อยละ 29.4 และชนิด transudates ร้อยละ 64.7 การเพิ่มความหนาแน่นของ extrapleural fat พบในชนิด exudates ร้อยละ 64.7 และในชนิด transudates ร้อยละ 28.6 ไม่พบลักษณะการกระจายตัวของน้ำในช่องเยื่อหุ้มปอดแบบไม่อิสระการหนาตัวของเยื่อหุ้มปอดแบบก้อนนูน และการหนาตัวของ extrapleural fat ในน้ำในช่องเยื่อหุ้มปอดชนิด transudates ความไว ความไวจำเพาะ และความแม่นยำของการหนาตัวของ extrapleural fat ในการแยกชนิดของน้ำในช่องเยื่อหุ้มปอด คิดเป็นร้อยละ 29, 100 และ 41 และในการเพิ่มความหนาแน่นของ extrapleural fat คิดเป็นร้อยละ 65, 71 และ 66 ตามลำดับ

วิจารณ์และสรุป : *การกระจายตัวของน้ำในเยื่อหุ้มปอดแบบไม่อิสระ การหนาตัวของเยื่อหุ้มปอดแบบก้อนนูน และการหนาตัวของ extrapleural fat บ่งชี้ว่าน้ำในช่องเยื่อหุ้มปอดน่าจะเป็นชนิด exudates อย่างมาก ส่วนค่าเฉลี่ยของน้ำในช่องเยื่อหุ้มปอดที่วัดได้จากการตรวจด้วยเครื่องเอกซเรย์คอมพิวเตอร์นั้นไม่มีความแม่นยำในการแยกชนิดของน้ำในช่องเยื่อหุ้มปอด*

คำสำคัญ : *น้ำในช่องเยื่อหุ้มปอด, transudate, exudate, เอกซเรย์คอมพิวเตอร์.*

Pleural effusion is one of the most frequent findings of thorax abnormality. Characterization of the pleural effusion into exudates or transudates is crucial for the diagnosis of various pathologies. Thoracentesis is the gold standard method to differentiate exudates from transudates.

Transudates are caused by the imbalance of microvascular pressure and plasma oncotic pressure. Common causes of transudative pleural effusions are heart failure, hepatic cirrhosis and hypoalbuminemia. Exudative pleural effusions are usually secondary to diseases of the pleura with accompanying increase in capillary permeability or decrease in lymphatic flow. Common causes of pleural exudates are infection and neoplasms. [1]

Computed tomography is non-invasive method frequently used for assessment of chest pathology. It has been reported that some findings in contrast-enhanced CT may help distinguishing pleural exudates from pleural transudates. [2 - 7]

The purpose of our study was to assess the accuracy of CT findings for differentiation of pleural exudates from transudates.

Materials and Methods

We retrospectively reviewed the patients who had pleural effusions and obtained contrast enhanced chest CT and thoracentesis from March 2005 to August 2007 at King Chulalongkorn Memorial Hospital. Diagnostic thoracentesis was performed within 2 weeks before or after the CT examination. When a patient had more than one thoracentesis, the one performed closer to the CT study was considered. The laboratory data for diagnosis of the pleural fluid obtained from thoracentesis included pleural fluid lactate dehydrogenase (LDH), pleural total protein, serum LDH and serum total protein values.

We excluded the patients who previously underwent pleural drainage tube placement or pleurodesis, or had inadequate laboratory data of pleural fluid from thoracocentesis.

Forty-one patients were examined with contrast-enhanced CT and diagnostic thoracentesis. There were 24 male and 17 female patients, aged 10 - 94 years (means 54 years).

Pleural effusions were classified as exudates or transudates based on Light's criteria. [8] An exudate was considered if pleural effusion had at least one of these three criteria: (a) pleural fluid protein to serum protein ratio > 0.5; (b) pleural fluid LDH to serum LDH ratio > 0.6; or (c) pleural fluid LDH greater than two-thirds of the upper limit of normal serum LDH. If the effusion did not meet any of these three criteria, it was considered transudate.

Presence of infectious organisms and cytological examination of the pleural effusion were also reviewed. Final diagnosis of pleural effusions was performed based on clinical findings, pleural fluid analysis, and pleural biopsy. Pleural effusions were diagnosed as: (a) malignant pleural effusion when the effusion was associated with malignancy that showed positive pleural cytology or biopsy; (b) effusion associated with malignancy when the patient had underlying malignancy but pleural cytology or biopsy of effusion was negative; (c) empyema when the pleural effusion from thoracentesis revealed macroscopic pus or had positive Gram stain or culture; (d) parapneumonic effusion when the effusion was associated with pulmonary infections but did not meet the criteria for empyema; (e) pleural effusion related

to benign known cause such as congestive heart failure, liver cirrhosis, pulmonary embolism or SLE when pleural effusion combined with clinical, thoracentesis and laboratory test correlated with these conditions.

Chest CT scans were performed on Somatom sensation 16-scanner (Siemens Medical Solution, Germany), using 120 kV, 100 mAs, 16 x 1.5 mm collimation, and 5-mm section thickness. CT scans were acquired during a single breath hold with the patient lying in supine position, extending from the lung apices to the adrenal glands. All studies were obtained 70-100 ml of non ionic contrast media at a rate ranging from 3 - 5 ml/sec.

The CT images were reviewed by a chest radiologist who was blinded to the final diagnosis of the pleural effusion.

The CT scans were evaluated for the presence and extent of pleural effusion. When the pleural effusion was bilateral, CT was evaluated only on the side that obtained thoracentesis. An effusion was classified as loculation if it had septations, compartmentalized or accumulated in a fissure or non-dependent portion of the pleura or showed a convex shape facing in the lung parenchyma. If the pleural fluid accumulated in the dependent portion with concave shape, it was classified as free distribution. The attenuation value of the pleural effusion was evaluated from three CT slices with greatest amount of fluid, and the maximum attenuation value in Hounsfield unit (HU) of these three slices was collected and averaged.

Parietal pleura, herein referred to combined mesothelial and submesothelisal supportive fibroelastic layers, was evaluated for pleural thickening. The pleura was considered thickening when it was thicker than 2 mm. Pleural thickening was also characterized as diffuse versus focal and nodular versus smooth. The mediastinal pleura was whether involved was also recorded.

Extrapleural fat was evaluated for thickness and attenuation. Extrapleural fat was considered thickened if it was thicker than 2 mm. [3] Attenuation of extrapleural fat was classified as normal fat attenuation or increased attenuation comparing to the subcutaneous fat.

Statistical analysis

Statistical analysis was performed using SPSS version 11.5. Continuous variables were expressed as mean $\pm$ SD. Mean value of HU were compared between groups by Student's *t* test. Two-tailed $p < 0.05$ was considered statistically significant.

Sensitivity and specificity of attenuation values in different cutoff points were calculated. Receiver operating characteristic (ROC) curve was done to evaluate the optimal cutoff points of attenuation value in differentiation exudates from transudates and to determine accuracy by using the area under the curve (A_z).

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each CT finding to detect the presence of pleural exudates were calculated.

Results

Forty-one patients had pleural effusion analysis, 34 were exudates and 7 were transudates. Cytology was positive for malignancy in 8 patients whereas 18 patients had underlying malignancy, but

the cytology was negative. All the eight patients with positive cytology showed exudative pleural effusions. The final diagnoses of the 41 patients are shown in Table 1.

Eight patients had benign effusions; two of these were associated with congestive heart failure; and the rest were related to chronic pyelonephritis, venous thrombosis, arthritis, SLE, sepsis and pyopericarditis each.

Pleural effusions were bilateral in 22 patients. Pleural effusions were analyzed from thoracentesis on the right side in 28 and on the left side in 13 patients. Eight patients had small amount of effusions, 13 had moderate amount and 20 had large amount of pleural effusions. The distribution of effusions was free in 23 patients and was loculated in 18 patients. All loculated effusions were exudates.

The mean attenuation value of exudates was 14.8 ± 5.8 HU (ranged 6.7 - 37.8 HU). The mean attenuation value of transudates was 10.7 ± 5.1 HU (ranged 5.9 - 20.9 HU). There was no significant difference of the mean attenuation values between these two groups (p = 0.09). ROC curve for the accuracy of attenuation values in the identification of exudates is shown in Figure 1. The optimal threshold value for the exudates was determined to be 11.75 HU, which demonstrated a sensitivity of 79.4% and specificity of 71.4% (Table 2).

Pleural thickening was present in 22 patients, 21 (61.8%) were exudates. The thickness of the thickened pleural was ranged from 2 mm to 2 cm. Parietal pleura was affected in every case. Mediastinal pleura was thickened in 11.8% of exudates and 14.3% of transudates. (Fig. 2) (Table 3). Of 22 patients, the thickened pleura was diffuse smooth thickening in 12 (Fig. 3); diffuse nodular thickening in 3 (Fig. 4); focal smooth thickening in 2 and focal nodular thickening in 5 (Table 4).

Table 1. Diagnosis of pleural effusions.

Diagnosis	No. of effusions	No. of exudates	No. of transudates
Malignancy	26	23	3
Lung	5	5	0
Lymphoma	8	8	0
Breast	3	2	1
Gastrointestinal	7	6	1
Genitourinary	1	1	0
Leukemia	1	1	0
Unknown primary	1	0	1
Empyema	2	2	0
Parapneumonic effusion	5	5	0
Effusion related to benign known cause	8	4	4
Total	41	34	7

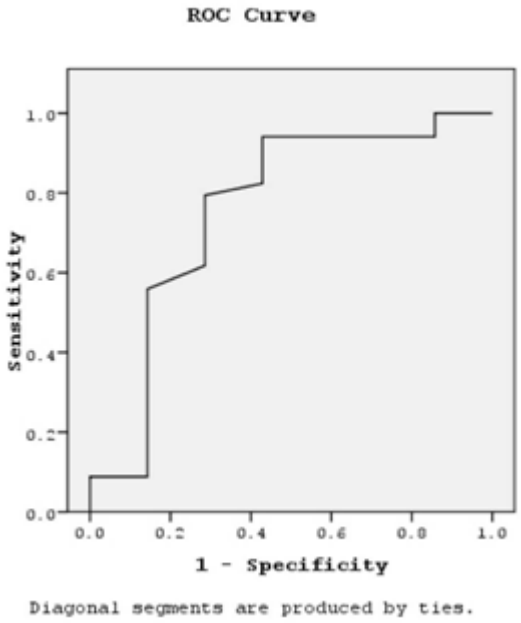

Figure 1. ROC curve plotting 1- specificity (x axis) against sensitivity (y axis). Overall accuracy was moderate with area under the curve of 0.76

Table 2. Sensitivity and specificity for exudates at various HU levels.

Criterion HU	Sensitivity	Specificity
≥ 4.90	100	0
≥ 6.85	97.1	14.3
≥ 7.85	94.1	42.9
≥ 9.70	91.2	57.1
≥ 10.55	85.3	57.1
≥ 11.75	79.4	71.4
≥ 12.05	73.5	71.4
≥ 12.70	61.8	71.4
≥ 12.95	52.9	85.7
≥ 13.25	47.1	85.7
≥ 13.90	41.2	85.7
≥ 14.75	35.3	85.7
≥ 15.50	29.4	85.7
≥ 16.30	23.5	85.7
≥ 17.55	17.6	85.7
≥ 20.20	11.8	85.7
≥ 22.85	8.8	100
≥ 31.40	2.9	100

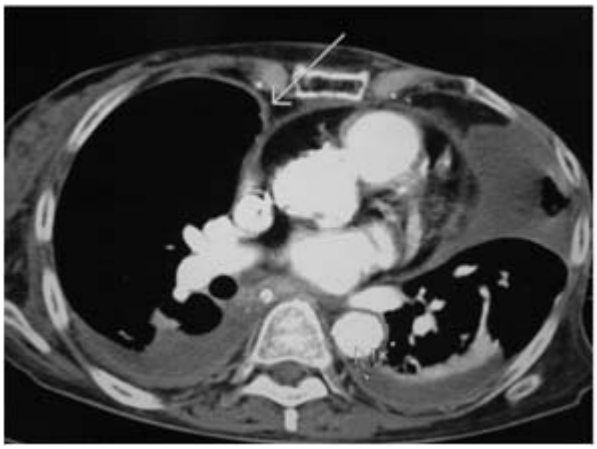

Figure 2. A 66-year-old woman with diffuse large B-cell lymphoma, contrast-enhanced CT scan shows right mediastinal pleural thickening (arrow) and bilateral parietal pleural thickening. Bilateral pleural effusions, loculated on the left, are also noted.

Table 3. Site of pleural thickening.

Diagnosis	Pleural thickening	
	Parietal	Mediastinal
Malignant pleural effusion	8	2
Effusion associated with malignancy	8	1
Empyema	2	0
Parapneumonic effusion	3	1
Effusion related to benign cause	1	1
Total	22	5

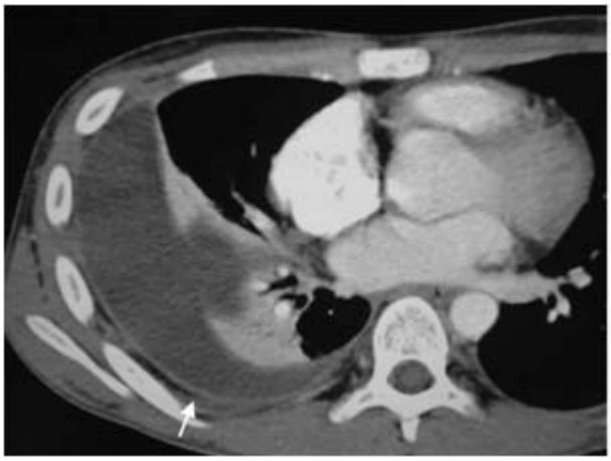

Figure 3. A 16 year-old man with ANLL and septicemia, contrast-enhanced chest CT shows diffuse smooth parietal pleural thickening and increased attenuation of thickened extrapleural fat (arrow).

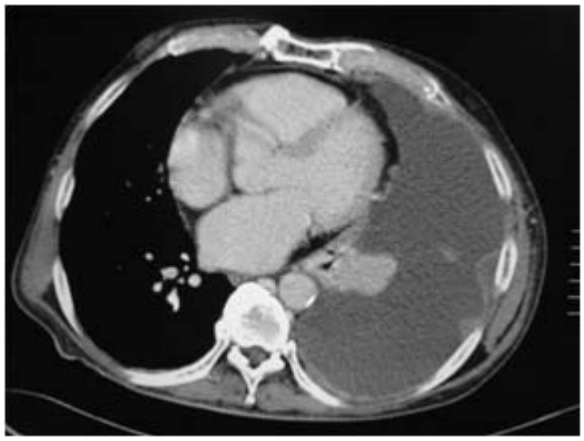

Figure 4. A 59-year-old man with colon cancer, contrast-enhanced chest CT of shows diffuse nodular pleural thickening.

Table 4. Characteristic of pleural thickening.

Diagnosis	No	Pleural thickening			
		Diffuse		Focal	
		Smooth	Nodular	Smooth	Nodular
Malignant pleural effusion	8	4	1	1	2
Effusion associated with malignancy	8	3	1	1	3
Empyema	2	2	0	0	0
Parapneumonic effusion	3	2	1	0	0
Effusion related to benign cause	1	1	0	0	0
Total	22	12	3	2	5

Extrapleural fat was thickened in 10 patients, ranged from 2.7 to 6.8 mm, and all (29.4%) were exudates. The attenuation of extrapleural fat was increased in 22 exudates (64.7%) and in 2 transudates (28.6%). Thickening and attenuation of extrapleural fat in all patients are shown in Table 5.

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of each finding e.g. attenuation value of pleural effusion > 15 HU, loculation of effusion, pleural thickening, extrapleural fat thickening and increased attenuation of extrapleural fat was shown in Table 6.

Discussion

Characterization of pleural effusion into exudates or transudates is helpful in determining the nature of the disease and clinical management. When transudative effusion is present, the treatment is directed toward the underlying cause. Whereas exudative pleural effusion reflects pathology of the pleura, further investigation to determine the cause or treatment is required.

Exudation is secondary to disease of the pleura with increase in capillary permeability or lymphatic obstruction, whereas, transudation is

Table 5. Extrapleural fat thickening and attenuation.

	No thickening		Thickening	
	Normal fat attenuation	Increased attenuation	Normal fat attenuation	Increased attenuation
Malignancy	2	1	0	5
Effusion associated with malignancy	9	6	0	3
Empyema	0	1	0	1
Parapneumonic effusion	2	2	0	1
Effusion related to benign cause	6	2	0	0
Total	19	12	0	10

Table 6. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of each CT finding for diagnosis of exudative effusions.

CT findings	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)	Accuracy (%)
Attenuation value of pleural fluid > 15 HU	32	86	92	26	41
Loculation of pleural fluid	53	100	100	30	61
Parietal pleural thickening	62	86	95	32	66
Mediastinal pleural thickening	12	86	80	17	24
Nodular pleural thickening	24	100	100	21	37
Extrapleural fat thickening	29	100	100	23	41
Increased attenuation of extrapleural fat	65	71	92	29	66

caused by an imbalance of the hydrostatic and osmotic pressure. As a result, pleural exudates are associated with increased level of pleural fluid protein and LDH according to Light's criteria. [8] Greater attenuation of exudative pleural effusion on CT is then anticipated. In the study of Nandalur *et al*. [2] in 145 patients reported that the mean attenuation of exudates (17.1 HU) is significantly higher than transudates (12.5 HU). The optimal threshold value was 13.4 HU, with 83.2% sensitivity and 70.5% specificity for detection of exudates effusion. In contrast to the study of Abramowitz *et al*., 13 exudates had negative attenuation; therefore, the mean attenuation of exudates (7.2 HU) was lower than of transudates (10.1 HU). The optimal threshold value for exudates in their study was determined to be < 8.5 with sensitivity of 55.1% and specificity of 68.2%. [9]

In our study, the optimal threshold value for exudates was determined to be 11.75 HU, which

showed a sensitivity of 79.4% and specificity of 71.4%. Exudates exhibited higher attenuation value than transudates, but there was no significant difference in mean attenuation values between transudates and exudates (p = 0.09). The overall accuracy of CT attenuation values was only moderate (A_z = 0.76). Similar to the study of Nandalur *et al*. and Abramowitz *et al*., the attenuation of effusion in CT has little role in stratifying pleural effusions as exudates or transudates.

In normal subjects, a 1-2-mm-thick pleural line at intercostal region seen on CT represent the combined thickness of visceral and parietal pleura, the fluid-filled pleural space, endothoracic fascia and innermost intercostal muscle. [10] Pleural thickenings are caused by various active and inactive processes, especially infection, hemothorax and malignancy. In normal patients, paravertebral intercostal veins could mimic pleural thickening. [10] Typically, the veins do not indent the pleura and seen only in segments. [10] Aquino *et al*. [3] examined 86 patients with contrast-enhanced CT and found that parietal pleural thickening was almost invariably an indicator of exudates, with sensitivity of 61% and specificity of 96%. Waite *et al*. also found pleural thickening only in exudates (42% sensitivity, 100% specificity). [4] Arenas-Jimenez *et al*. [6] reported that pleural thickening and pleural nodules were present only in exudative effusion with 42% sensitivity and 100% specificity. However, Abramowitz *et al*. reported 36% of transudates had pleural thickening. In our study, there was only one transudate (14.3%) had diffuse pleural thickening. All nodular pleural thickening, either focal or diffuse, was seen only in exudates. Leung et al., reported that thickening of mediastinal pleura was suggestive of malignant pleural disease, that were usually exudates (56% sensitivity, 88% specificity). [11] In our study, the mediastinal pleural thickening was present in 11.8% of exudates and 14.3% of transudates. The other CT findings that were helpful in differentiating malignant from benign pleural diseases included circumferential pleural thickening, nodular pleural thickening, and parietal pleural thickening greater than 1 cm. [11]

When there is adhesion between visceral and parietal pleura, loculation of effusion occurs i.e. the effusion does not shift in the pleural space, Similar to our study, Arenas-Jimenez *et al*. [6] reported that loculation of pleural effusion was present only in exudative effusion. On the contrary, Abramowitz et al. found loculated effusion in 36% of transudates compared with 59% of exudates. This is possibly due to pre-existing pleural adhesion from any causes which results in loculation of effusion.

The extrapleural fat, serving as the cleavage plane during decortications, separates the parietal pleura from the endothoracic fascia and innermost intercostal muscle. Normally, it is 2 mm or less in thickness. [4, 10] Waite *et al,* examined 85 patients and found 40% of empyema and 10% of malignant pleural effusion had pleural thickening more than 2 mm. [4] In their study, similar to our study, none of transudative pleural effusion had this finding. Despite empyema resolved; however, thickening of extrapleural fat often persisted. [4] Therefore, in patients with previous history of empyema, evaluation of thickening of extrapleural fat should be cautious.

Edema, lymphatic distension, infiltration with inflammatory cells or granulation tissue can cause increased attenuation of extrapleural fat and can be

mistaken for a pleural fluid collection. [4, 7, 12] Waite *et al*. [4] , Arenas-Jimenez's *et al*. [6] and Takasugi *et al*. [7] found that the attenuation of extrapleural fat was increased exclusively in exudative effusions. In our study, increased attenuation of extrapleural fat was found in 28.6% of transudates which shows 65% sensitivity and 71% specificity for differentiation of exudates from transudates. When the empyema resolved, in contrast to thickening of the extrapleural fat which usually persist, the attenuation of the extrapleural fat return to homogeneous fat attenuation. [4]

There were several limitations in our study. First, it is a retrospective study, and the thoracentesis and CT were not performed in the same time. In the setting of congestive heart failure who is on dieresis, transudate can be misclassified as exudate based on Light's criteria. Second, there were small numbers of population, particularly the ones with transudates as a result of selection bias. In patients with clinically suggestive of transudative effusions such as congestive heart failure were not generally performed CT and thoracentesis. In addition, we also excluded the patients who previously underwent placement of a pleural drainage tube to avoid any changes of extrapleural space from intervention. Lastly, the attenuation value of pleural fluid in small effusion may not be accurate.

Conclusion

Loculation of pleural effusion, nodular pleural thickening and extrapleural fat thickening at contrast-enhanced CT are highly suggestive of the presence of pleural exudates. CT attenuation values of exudates are higher than transudates, but there were no clinical value in differentiating exudates from transudates.

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