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Sonographic Septation as One Predictor for Pleural Drainage in Patients with Non-purulent Parapneumonic Effusions

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Background: The American College of Chest Physician (ACCP) has identified 4 categories of parapneumonic effusion (PPE) to guide treatment. The modality in assessing anatomy of pleural fluid is not well-defined, making differentiation of category 2 from category 3 PPE difficult. We investigated whether sonographic septation predicts category 3 PPE in guiding early pleural drainage. **Methods:** Medical records of patients with lung abscess or pneumonia at admission were reviewed retrospectively. All patients had a plain chest radiograph upon admission. Patients classified as AACP category 2 or 3 who underwent chest sonography with thoracentesis revealing non-purulent parapneumonic effusions with neutrophils predominance were included. Inter-observer variations in determining PPE category were analyzed. Further, positive predictive value (PPV), relative risk (RR) and reading agreement of positive sonographic septation in predicting category 3 PPE were determined. **Results:** 51 patients of the total 97 recruited had sonographic septation. The reading agreement between thoracic radiologists in determining the category of pleural fluid by plain chest radiograph was low with a kappa coefficient (κ) of 0.29. In contrast, reading agreement of positive sonographic septation was substantial (κ = 0.73). A significantly higher PPV for category 3 effusion was observed in patients with sonographic septation (86.3%) compared to those with no septation (43.5%) ($p < 0.001$). The RR of category 3 PPE with sonographic septation was 1.98 (95% CI: 1.40-2.81; $p<0.001$). **Conclusions:** Sonographic septation is a useful sign in predicting category 3 PPE, and may in conjunction with plain chest radiograph, enable a more accurate diagnosis or screening way of patients with lung abscess and pneumonia.

Key words: pneumonia, parapneumonic effusion, sonography, thoracocentesis

Abbreviations: ACCP = American College of Chest Physician; CI= confidence interval; PE = pleural effusion; PPE = parapneumonic effusion; PPV = positive predictive value; RR = relative risk; SD = standard deviation

INTRODUCTION

Parapneumonic effusion (PPE) refers to any effusion associated with pneumonia or lung abscess. Twenty to forty percent of hospitalized patients with pneumonia have a PPE.[1] Treatment of PPE includes appropriate antibiotic therapy and adequate drainage of the pleural fluid. Physicians commonly delay diagnosis and drainage for patients with PPE because of unclear clinical features, resulting in increased hospitalization costs.[2] In 1998, an expert panel selected by the American College of Chest Physicians, the American Thoracic Society, American College of Radiology, American Association of Thoracic Surgeons, and the Infectious Disease Society of America developed a guideline to evaluate the risk of poor outcome in patients with PPE.[3-5] In the guideline, PPEs are categorized according to anatomy, chemistry and bacteriology of the pleural fluid into category 1, 2, 3 and 4 as: Category 1, minimal, free-flowing effusion (<10 mm) with unknown pH, Gram stain and culture results;

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Category 2, small to moderate free-flowing effusion (≥10 mm and < 1/2 hemithorax) with a pH ≥7.20 and negative Gram stain and culture ; Category 3, large, free-flowing effusion (≥ 1/2 hemithorax), loculated effusion, or effusion with thickened parietal pleura, or a pH <7.20, or positive Gram stain and/or culture; Category 4, empyema (i.e. pus in the pleural fluid).[4,5] The expert panel recommends that patients with category 1 or 2 PPE may not require drainage, whereas drainage is recommended for patients in category 3 and 4[4,5]

Plain chest radiograph may not accurately assess the amount or characteristics of the pleural fluid, especially for subpulmonic effusions, nondependent loculations, or effusion assessed in supine position.[4] The best modality to assess the characteristics of the pleural fluid is not clearly-defined in the guideline, leading to a difficult differentiation between category 2 and category 3 PPE which is important in guiding appropriate intervention. Sonographic septation has been proved to predict prolonged hospital stay and the need for chest tube drainage in acute thoracic empyema.[6]

A diagnostic thoracentesis is almost impossible for category 1 because of the minimal, free-flowing effusion (<10 mm) defined in the ACCP guideline.[4,5] Moreover, the determination of a category 4 PPE (i.e. empyema) is straightforward as the aspirated pleural fluid appears to be pus.[4,5] Given the limitation in differentiating category 2 PPE based on plain chest radiograph and the lack of study on the application of sonographic septation to categorize PPE, the aim of this study focusing on patients with category 2 and 3 PPE to determine if sonographic septation serves as a useful and complementary modality in differentiating these two categories for assisting determination of early pleural drainage. The difference of comorbidity, hospital day, rate of acute respiratory failure, and mortality between sonographic septation and non-septation PPE will also be compared in this study.

MATERIALS AND METHODS

Study subjects

We retrospectively reviewed medical records of patients with diagnosis of lung abscess or pneumonia, with pleural effusion, who underwent chest sonography and thoracentesis between January 2002 and December 2008 at the Tri-Service General Hospital, a tertiary referral center in Taiwan. All patients with clinical diagnosis of PPE were assessed. Patients were eligible if the diagnostic thoracentesis recovered exudative pleural fluids with neutrophils predominance. Patients who had PPE were categorized by their chest radiographic findings and characteristics of the pleural fluid.[4] Patients were excluded if their pleural fluid showed transudates or lymphocyte predominance, or was proven to be tuberculosis-related or empyema (i.e pus in the aspirated pleural fluid) defined in the ACCP guideline.[4] Patients with category 2 or 3 PPE were selected as they all underwent chest sonography and a diagnostic thoracentesis which allowed us to correlate sonographic findings with results of thoracentesis. The results of sputum cultures, pleural fluid cultures, patient's co-morbidity, hospital stay, rate of acute respiratory failure, and mortality were also determined from medical records. This study was approved by Tri-Service General Hospital institutional review board (TSGHIRB: 099-05-258).

Imaging studies of the chest

Two board-certified thoracic radiologists with at least10-year experience were blinded to patients' clinical information while interpreting plain chest radiograph to assign patient's pleural space anatomy into A1 or A2 category of PPE according to ACCP guideline.[4] In case of any discrepancies between two thoracic radiologists, a senior board-certified chest physician will be required to review the chest imaging studies to determine final interpretation.

For chest sonography, patients were examined on upright sitting position or on lateral decubitus position using a real-time ultrasound scanner (Toshiba SSA-340A; Toshiba; Tokyo, Japan) with 3.75 MHZ sector transducers, followed by a diagnostic thoracentesis if the width of pleural effusion exceeded 10 mm. All sonographic pictures of pleural fluid of recruited patients were saved in a JPG format. Sonographic septation was determined by two board-certified chest physicians blinded to the patients' clinical information. In case of any discrepancies between two chest physicians, a senior board-certified chest physician will be required to determine the presence or absence of septation.

Sonographic septation in pleural effusions was defined as the presence of fibrinous strands (Fig.1A) or web-like fibrinous strands in the pleural effusion.[6,7] (Fig. 1B). as opposed to a non-septated pleural effusion (Fig. 1C).

Pleural effusions recovered by diagnostic thoracentesis were aliquoted into different collecting tubes. All test specimens were sent to the laboratory for analysis of lactate dehydrogenase, total protein, glucose, total leukocyte counts, differential leukocyte counts, bacterial cultures, Gram stain, tuberculosis culture, acid-fast stain, and pH by a blood gas analyzer.

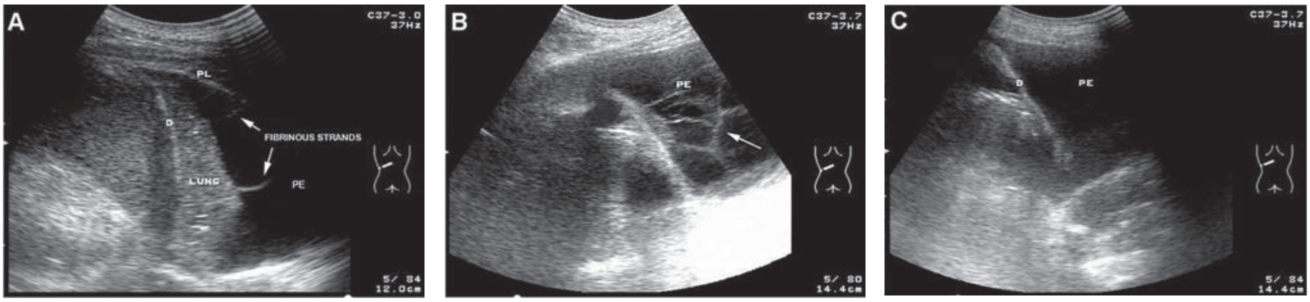

Fig. 1 A sonography of the chest shows fibrinous strands (arrows) in a 32-year-old man with pneumonia and parapneumonic effusion of the left thorax (A), web-like septa (arrow) in a 75-year-old man with pneumonia and parapneumonic effusion of left thorax (B), and a simple pleural effusion of the left thorax in a 88-year-old man with pneumonia (C). PE: pleural effusion; D: diaphragm; PL: pleura.

Table 1 Patient demographics and PPE categorization.

Characteristics	Total n=97	Sonographic septation Positive n=51	Sonographic septation Negative n=46	*p*-value
Gender, No.				0.316
Female	22	9	13	
Male	75	42	33	
Age, yr		61.2±19.1	65.6 ±16.8	0.239
Category 2 effusion				
A1 B0 C0 P0	33	7	26	
Category 3 effusion				
A1 B0 C1 or P1	12	6	6	
A1 B1 C0 P0	2	1	1	
A1 B1 C1 and/or P1	4	3	1	
A2 B0 C0 P0	14	10	4	
A2 B0 C1 and/or P1	27	19	8	
A2 B1 C0 P0	1	1	0	
A2 B1 C1and/or P1	4	4	0	
Mortality, %	11.5	10.0	13.0	0.883

A1: small to moderate free-flowing effusion (> 10 mm and <1/2 hemithorax); A2: large, free-flowing effusion (≥ 1/2 hemithorax), or loculated effusion, or effusion with thickened parietal pleura; B0: negative culture and Gram stain of pleural effusion; B1: positive culture or Gram stain of pleural effusion; C0: pleural effusion pH ≥ 7.20 ; C1: pleural effusion pH < 7.2; P0: pleural effusion glucose ≥ 60 mg/dL; P1: pleural effusion glucose < 60 mg/dL.

Statistical analysis

Data were expressed as mean±standard deviation (SD). Continuous variables between groups were compared by the Student's t-test. The chi-square test was used to test the difference between two groups with respect to categorical variables. Positive predictive value (PPV), relative risk (RR) and corresponding 95% confidence interval (CI) of positive sonographic septation in predicting effusion category were calculated. The agreement between two observers in determining the anatomy of pleural fluid was evaluated by kappa statistic. All analyses were performed using the SPSS 17.0 software package (SPSS Institute Inc., Chicago, USA). All statistical analyses were two-tailed using a significance level of 0.05.

RESULTS

97 patients were recruited. 51 patients had sonographic septations and 46 patients had no sonographic septations. Patient demographics and categorization of PPE are shown in Table 1. In the no-septation group, 26 and 20 patients were in category 2 and 3, respectively. In the septation group, 7 and 44 patients were in category 2 and 3, respectively. There were no significant difference in gender distribution, mean age and mortality between groups.

Laboratory characteristics of pleural effusions and sonographic features are shown in Table 2. Glucose level ($P = 0.002$) and pH value ($P = 0.002$) in pleural effusions were significantly lower in the sonographic septation group than in the no-septation group. Total protein level was significantly higher in the sonographic septation group.

In patients with PPE, the presence of sonographic septation was more predictive for category 3 PPE (86.3% vs. 43.5%, P < 0.001). The sensitivity, specificity, PPV,

Table 2 Correlations between laboratory characteristics of pleural effusions with sonographic features.

Characteristics	Sonographic septation Positive (n = 51)	Sonographic septation Negative (n = 46)	*p*-value
LDH, IU/dL	1692±1667	1225±1630	0.167
Total protein, g/dL	4.60±0.92	4.03±1.07	0.006
Glucose, mg/dL	62.10±59.70	106±73.80	0.002
pH	7.39±0.53	7.69±0.55	0.002
Total leukocyte count, cells/μL	8221±11436	9257±12787	0.674
% Neutrophils	80.50±12.40	75.50±13.20	0.056
% Lymphocytes	12.30±10.90	14.90±12.00	0.279
% Mesothelial cells	3.47±4.30	2.60±4.58	0.571
% Macrophage	7.65±5.36	8.05±7.10	0.782

Table 3 Positive predictive value and relative risk of positive septation in predicting PPE category 3 according the ACCP guideline.

	Sonographic septation	Patients with PPE (%) Category 2	Patients with PPE (%) Category 3	RR†	(95% CI)
All patients	Positive (n=51)	13.7	86.3‡	1.98	(1.40-2.81)**
	Negative (n=46)	56.5	43.5	1.00	
Patients depend on radiological finding only	Positive (n=17)	41.2	58.8‡	4.41	(1.63-11.9)*
	Negative (n=30)	86.6	13.4	1.00	

† RR, relative risk of positive septation vs. negative septation in predicting category 3.

‡ positive predictive value

* P = 0.001; ** P < 0.001

and negative predictive value of sonographic septation in category 3 PPEs were 68.8%, 78.8%, 86.3%, and 56.5% respectively (Table 3). The risk of category 3 effusion in PPE with sonographic septation tended to be greater than the risk of category 3 effusion in PPE with no sonographic septation (RR 1.98, 95% CI: 1.40-2.81). The interobserver agreement reached a κ of 0.73 between two chest physicians, whereas interobserver agreement was poor between two thoracic radiologists for chest radiographs in determining the anatomy of pleural effusion with a $\kappa = 0.29$.

A total of 47 of 97 (48.5%) patients had normal bacteriologic and chemical results of pleural fluids (B0C0P0). They were categorized solely on the anatomy of pleural fluids. 14 and 33 patients were categorized to category 3 (A2B0C0P0) and 2 (A1B0C0P0) based on the anatomy of pleural fluids. For patients whose classification was based solely on the anatomy of pleural fluids, the risk for falling into category 3 PPE with sonographic septation tended to be greater than those without sonographic septation (RR 4.41, 95% CI: 1.63-11.9). As shown in Table 3, the PPV for category 3 was 58.8% with positive sonographic septation.

DISCUSSION

Chest sonography is a convenient method in guiding thoracentesis.[8,9] Sonographic patterns may be valuable in the diagnosis of pleural effusions in certain disease.[10,11] Sonographic septation is present in pleural effusion from a variety of etiologies, such as PPE[12], tuberculous pleuritis[10,12,13], malignant pleural effusion,[14] empyema,[6] and hemothorax,[7] but its clinical application in the management of PPE remains unclear. Although both sonographic septation and non-septation pleural effusions were observed in categories 2 and 3 PPE, a significantly higher PPV for sonographic septation was observed when compared to that for sonographic non-septation (86.3% v.s. 43.5 %) in category 3 PPE, suggesting that sonographic septation may be a good tool to differentiate category 2 to category 3 PPE. Given this result, we proposed that chest sonography might serve as a useful tool of investigation for patients with PPE. Kearney et al reported that 24 patients with sonographic septated pleural effusion, only 2 of 24 patients were in stage 1 effusion[15], and 22 of 24 patients were in stage IIa or IIb according to the criteria established by Light *et al*.[16] Both studies suggested that sonographic septation is common in enhanced pleural infection. These observations were supported by a significant lower pleural pH value and glucose level, higher total protein level in sonographic septation group compared to the non-septation group.

In the present study, 48.5% of patients were categorized solely by the anatomy of pleural fluids as bacteriology and chemistry of their pleural fluids did not conclude a final PPE category. In this subgroup, there was a fairly high disagreement in interpreting the anatomy of pleural fluids between thoracic radiologists ($\kappa = 0.29$). Similar to previous observations, the poor agreement did not appear to be related to the lack of clinical experience but rather as a result of the difficulty in the reading of chest radiograph due to the amount of pleural effusion.[17,18] A fairly high agreement ($\kappa = 0.73$) was reached in sonographic reading for septation, suggesting that it is a more consistent and reliable imaging modality in characterizing pleural effusion. Nevertheless, the RR was 4.41 for sonographic septation as comparing with sonographic non-septation in category 3 effusion. Noted in this subgroup, sonographic sepation may remain a warning sonographic sign in category 3 PPE despite of a relatively low PPV.

In this study, we did not include category 1 PPE because of a potential difficulty in assessing minimal pleural effusion, in performing a diagnostic thoracentesis and in measuring sonographic echogenicity. Category 4 effusions (empyema) were also excluded from this study as it was readily assured once pus in pleural fluid was observed regardless findings from other diagnostic measures. The challenge then remained for the differentiation of a category 2 PPE from a category 3 one that mandates a surgical drainage. Our results deemed to support that real-time chest ultrasound may serve a simple and effective modality with a reliable tool as sonographic septation in predicting category 3 PPE to guide an appropriate intervention.

PPEs may evolve depending on patients' clinical course, treatments offered or disease progression, and sonographic septation could predict the clinical course. Nonetheless, repeated thoracentesis has proven to change sonographic echogenicity from non-septation to septation.[19] We limited our analysis to findings of sonographic echogenicity, bacteriology, and biochemistry collected from the first diagnostic thoracentesis, assuming that early determination of PPE category may shorten patients' hospital course. However, it may be interesting to study further the clinical implications of changing sonographic echogenicity from non-septation to septation and vice versa along with patient's clinical course.

In conclusion, a high discrepancy existed in determining the anatomy of pleural fluids between thoracic radiologists. We demonstrated a strong correlation between sonographic septation and category 3 PPEs, suggesting that chest sonography may serve as a valuable modality in the differentiation of category 2 to 3 PPE to guide early treatment.

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COI DISCLOSURE

There were no conflicts of interest to be disclosed by all contributing authors of this manuscript.

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