Pleural Fluid Amino-Terminal Brain Natriuretic Peptide in Patients With Pleural Effusions

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BACKGROUND: Definite diagnosis of transudative or exudative pleural fluids often presents a diagnostic dilemma. The aim of this study was to evaluate whether amino-terminal brain natriuretic peptide (NT-proBNP) levels in pleural fluid has a diagnostic value for discriminating heart-failure-related pleural effusions from non-heart-failure effusions. METHODS: Sixty-six subjects (40 male, mean age 61 ± 18 y) with pleural effusions were included. Samples of pleural fluid and serum were obtained simultaneously from each subject. Biochemical analysis, bacterial and fungal culture, acid-fast bacilli smear and culture, and cytology were performed on the pleural fluid. RESULTS: Subjects with heart-failure-related pleural effusion had significantly higher pleural NT-proBNP levels than other subjects ($P < .001$). Pleural and serum NT-proBNP measures were closely correlated ($r = 0.90$, $P < .001$). An NT-proBNP cutoff value of ≥ 2,300 pg/mL in pleural fluid had a sensitivity of 70.8%, a specificity of 97.6%, and positive and negative predictive values of 94.4% and 85.4%, respectively, for discriminating transudates caused by heart failure from exudates. Eight heart-failure subjects were misclassified as exudates by Light's criteria, 5 of whom received diuretics before thoracentesis. All misclassified subjects had pleural NT-proBNP levels higher than 1,165 pg/mL, which predicted heart-failure-associated transudates with 95.8% sensitivity and 85.7% specificity. CONCLUSIONS: Pleural fluid NT-proBNP measurement in the routine diagnostic panel may be useful in differentiation of heart-failure-related pleural effusions and exudative pleural fluids with reasonable accuracy, especially in heart-failure patients treated with diuretics.
Key words: amino-terminal brain natriuretic peptide; NT-proBNP; heart failure; Light's criteria; pleural effusion. [Respir Care 2013;58(2):313–319.

Introduction

Pleural fluid is classically classified as a transudate or an exudate, which helps in determining the cause of pleural effusions. The criteria of Light et al are used as a first step to differentiate transudates from exudates in the workup of patients with pleural effusion.[1] However, these criteria have some limitations, especially in patients with heart failure and taking diuretics.[2,3] Imbalance of hydrostatic and osmotic forces caused by heart failure is the main reason that transudates and diuretic therapy limit the accuracy of the criteria, leading to misdiagnosis of pleural fluids.[4,5] Misdiagnosis of transudates as exudates may lead to unwarranted invasive interventions or delay in the ini-

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tiation of appropriate therapy. Although clinical judgment can aid in determining which patients with pleural effusion most likely have heart failure, the criteria of Light et al[1] are shown to be significantly superior to clinical presumption to separate heart-failure-associated transudates from exudates.[3] Thus, several other methods have been proposed to differentiate exudates from transudates, including the serum-effusion albumin difference (a difference of < 1.2 g/dL between the serum and pleural fluid albumin levels),[6] serum-effusion protein difference, pleural cholesterol concentration (pleural cholesterol > 60 mg/dL),[7] and pleural effusion/serum bilirubin ratio (a pleural fluid/serum bilirubin ratio > 0.6).[8] However, controversy exists as to which method is more accurate and effective.

Increased tension or stretching of the cardiac wall stimulates the synthesis and secretion of natriuretic peptides. The levels of both brain natriuretic peptide (BNP) and the amino-terminal proBNP (NT-proBNP) are significantly elevated in patients with heart failure. Thus, they are widely used in the diagnosis and management of heart failure.[9–12] Recent studies demonstrated that BNP and NT-proBNP levels were elevated in the pleural fluid of patients with heart failure and suggested that pleural fluid NT-proBNP might be useful in the diagnosis of pleural effusion resulting from heart failure.[2,13,14]

The aim of the study was to evaluate the diagnostic accuracy of pleural fluid NT-proBNP in differentiation of heart-failure-related pleural effusions from non-heart-failure-related effusions.

QUICK LOOK

Current knowledge

Pleural fluid is classically classified as a transudate or an exudate, which helps in determining the cause of effusions. The criteria of Light et al are used to differentiate transudates from exudates. Misdiagnosis of transudates as exudates may lead to unwarranted invasive interventions or delay in the initiation of appropriate therapy.

What this paper contributes to our knowledge

Plasma and pleural fluid amino-terminal brain natriuretic peptide (NT-proBNP) levels were significantly higher in patients with heart-failure-associated pleural effusion, compared to exudative pleural effusions. Measurement of NT-proBNP can improve accuracy in differentiating exudative and transudative pleural effusion.

Methods

This investigation conformed to the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee of Marmara University. All participants gave written informed consent before participating.

Seventy-five consecutive subjects with pleural effusions who were scheduled to undergo diagnostic thoracentesis were included prospectively into the study. The demographic and clinical parameters of the subjects were noted. Pleural fluid and serum samples were obtained simultaneously from each subject. Biochemical analysis (including lactate dehydrogenase (LDH), protein, albumin, glucose, blood urea nitrogen, and creatinine), bacterial and fungal culture, acid-fast bacilli smear, polymerase chain reaction test for *Mycobacterium tuberculosis*, and cytologic examinations were performed on all pleural fluid samples. Chest x-ray and electrocardiography were obtained from each subject. All subjects underwent echocardiographic examination to determine biventricular systolic and diastolic functions, together with pulmonary hypertension and pericardial effusion, if present. Any further diagnostic test, such as pleural biopsy, was performed at the discretion of the primary physicians.

The diagnosis of heart failure was based on the presence of symptoms and signs, including paroxysmal nocturnal dyspnea, orthopnea, rales, jugular venous distention, third heart sound, prominent murmur, and pretibial edema. The diagnosis was further confirmed by echocardiography and chest x-ray. Pleural effusion was attributed to heart failure when the subject had symptoms and signs of left ventricular failure, echocardiography study revealed systolic or diastolic dysfunction of the left ventricular, and the pleural effusion responded to appropriate diuretic therapy.

Measurement of NT-proBNP levels in serum and pleural effusion and all other biochemical analyses were carried out within 4 hours after specimen collection. NT-proBNP levels were measured by a monoclonal electrochemiluminescence immunoassay using an immunoassay analyzer (Elecsys, Roche Diagnostics, Mannheim, Germany) according to the manufacturer's protocol. The test has an intra-assay coefficient of variation of 0.8–3%. The detection range of the test is from 5 to 35,000 pg/mL.

Pleural effusions were categorized as either exudates or transudates, according to the criteria of Light et al[1] The fluid was defined as an exudate if it fulfilled at least one of the following criteria: pleural/serum ratio of total protein > 0.5, pleural/serum ratio of LDH > 0.6, or pleural LDH more than two thirds of upper normal limit of serum LDH.

Pleural effusions were diagnosed as malignant if malignant cells were detected on the cytologic examination of pleural fluid or pleural biopsy, or if the subject had a known malignancy and alternative diagnoses were excluded. Parapneumonic pleural effusion and empyema were defined as the clinical and radiological diagnosis of pneu-

Table 1. Blood and Pleural Fluid Characteristics of the Subjects

	Heart Failure (n = 21)	Malignant (n = 22)	Parapneumonic (n = 8)	Empyema (n = 7)	Tuberculosis (n = 5)	Others (n = 3)
Blood						
NT-proBNP, median (IQR), pg/mL	6,653 (2,324–21,869)	136 (51–392)	671 (266–2,105)	198 (123–1,583)	68 (43–216)	2,568
Protein, mean ± SD, g/dL	6.7 ± 1.1	6.9 ± 0.8	6.7 ± 1.1	6.7 ± 0.9	7.0 ± 1.0	5.4 ± 3.2
LDH, median (IQR), U/L	390 (316–536)	400 (313–572)	436 (263–598)	326 (253–413)	298 (243–986)	472
Pleural						
NT-proBNP, median (IQR), pg/mL	7,583 (1,883–16,085)	279 (110–452)	814 (465–2,135)	498 (98–1,107)	202 (81–409)	3,961
Protein, mean ± SD, g/dL	3.3 ± 1.8	4.6 ± 1.0	3.6 ± 2.2	4.0 ± 2.2	5.1 ± 1.3	2.9 ± 2.6
LDH, median (IQR), U/L	183 (161–362)	439 (215–660)	474 (334–626)	1,047 (300–1,918)	382 (240–598)	328
Pleural/Serum						
Protein ratio, mean ± SD	0.49 ± 0.21	0.66 ± 0.09	0.49 ± 0.32	0.59 ± 0.26	0.72 ± 0.11	0.50 ± 0.17
LDH ratio, mean ± SD	0.58 ± 0.36	1.02 ± 0.54	1.49 ± 1.43	3.20 ± 1.92	1.09 ± 0.74	0.69 ± 0.45
Albumin difference, mean ± SD, g/dL	1.73 ± 0.91	1.11 ± 0.37	1.45 ± 0.99	1.34 ± 0.96	0.44 ± 0.35	2.53 ± 1.37

NT-proBNP = amino-terminal pro-brain natriuretic peptide
LDH = lactate dehydrogenase

monia or positive bacterial culture in pleural fluid, together with other suggestive laboratory findings (pleural fluid pH and white-blood-cell count, and blood white-blood-cell count). Hepatic hydrothorax was defined as an effusion due to cirrhosis in the presence of ascites. Pleural fluid was categorized as tuberculous if *Mycobacterium tuberculosis* was found in pleural fluid, or granuloma in pleural biopsy, or an exudative lymphocytic effusion with high adenosine deaminase levels (> 40 U/L) cleared in response to anti-tuberculosis therapy. Other miscellaneous causes of pleural effusions were determined by clinical and laboratory data by the attending physician.

Nine subjects with pleural effusions of undetermined origin, effusions with more than one possible cause, or hemothorax were excluded in the analyses.

Statistical Analysis

Statistical analysis was performed by a commercially available statistical software package (SPSS 16.0, SPSS, Chicago, Illinois). Data are presented as mean ± SD. Because the blood and pleural fluid concentrations of NT-proBNP and LDH were not normally distributed, their values are presented as median and IQR. The Kruskal-Wallis test, Mann-Whitney U test, or Fisher exact test were used to assess the difference between different groups. The Spearman coefficient of rank correlation was used to evaluate the relation between NT-pro-BNP levels of plasma and pleural fluid. Receiver operating characteristic curve analysis was performed to determine the cutoff levels of pleural fluid NT-proBNP. A P value of .05 or less was regarded as statistically significant.

Results

Sixty-six subjects (40 male) with pleural effusions who were scheduled for diagnostic thoracentesis were consecutively included in the study. The mean ± SD and median age of the study group was 61 ± 18 years and 65 years. Twelve subjects had coronary artery disease, while 29 had hypertension, 11 had diabetes, and 12 had COPD. The causes of pleural effusions were as follows: malignancy 22 subjects (33.3%), heart failure 21 subjects (31.8%), parapneumonic 8 subjects (12.1%), empyema 7 subjects (10.6%), tuberculosis 5 subjects (7.6%), renal disease 2 subjects (3.1%), and liver cirrhosis 1 subject (1.5%). Most subjects with malignancy-associated pleural fluid had either primary or metastatic lung cancer. Among the 21 subjects with heart failure, 5 subjects (24%) had systolic heart failure, with a median left ventricular ejection fraction of 25%, while the remaining 16 (76%) had diastolic heart failure confirmed with echocardiography. Three subjects also had pericardial effusion, and 15 heart-failure subjects (71%) had pulmonary hypertension, with a median systolic pulmonary arterial pressure of 45 mm Hg.

Blood and pleural fluid NT-proBNP levels are shown in Table 1, together with LDH and protein levels. Subjects with pleural effusion due to heart failure had significantly higher pleural fluid NT-proBNP levels than others ($P < .001$) (Fig. 1). Pleural and serum NT-proBNP measures were closely correlated ($r = 0.90$, $P < .001$, Fig. 2). While there were not any significant differences between blood and pleural total protein levels among the groups, the pleural LDH levels, pleural/blood LDH ratio, and serum-pleural fluid albumin difference significantly differed ($P = .04$, $P = .004$, and $P = .02$, respectively).

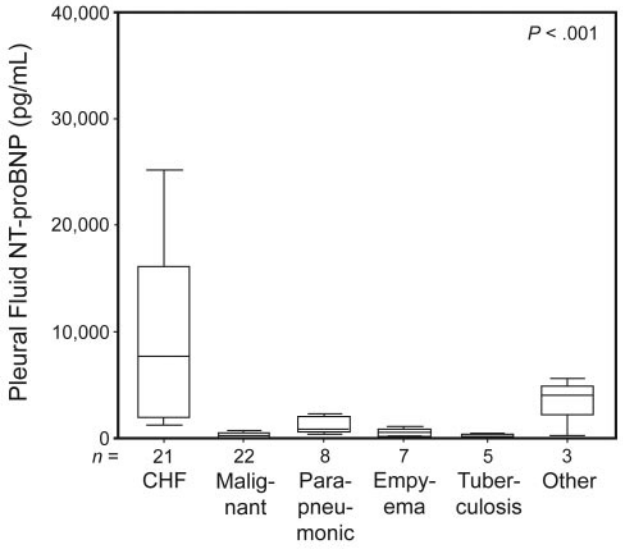

Fig. 1. The median and quartiles of pleural amino-terminal pro-brain natriuretic peptide (NT-proBNP) values according to etiology. CHF = congestive heart failure.

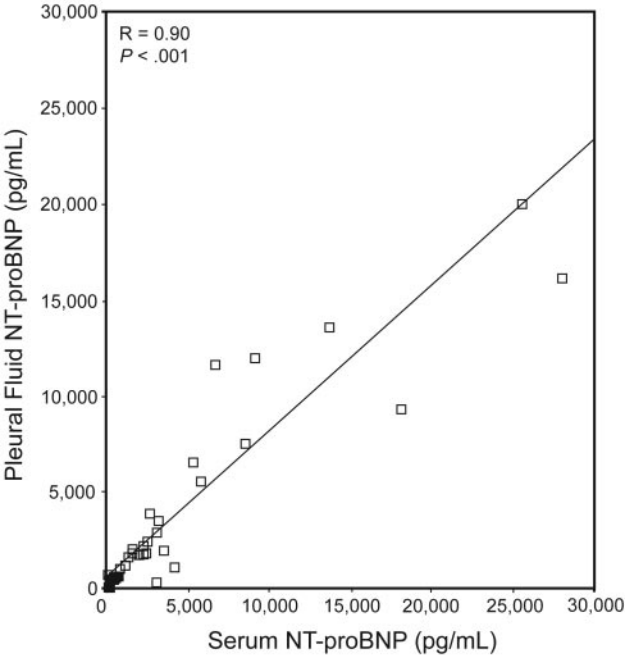

Fig. 2. Correlation of serum and pleural effusion level of amino-terminal pro-brain natriuretic peptide (NT-proBNP).

According to the criteria of Light et al,[1] 51 of the pleural fluids were exudates. The distribution of causes of pleural fluid according to transudate or exudate is presented in Table 2. Using the above criteria, 9 effusions were incorrectly classified as exudates (13.6%). Eight of these subjects had pleural effusion due to heart failure, and one had renal failure. Pleural fluid and serum parameters of true transudates, false exudates, and true exudates are shown in Table 3. The false exudates had significantly higher levels of pleural fluid and serum NT-proBNP compared to true exudates ($P < .001$ for both comparisons), while they had significantly lower levels of pleural fluid and serum NT-proBNP, compared to true transudates ($P = .008$ and $P = .01$, respectively). Five of the false exudates received diuretics before thoracentesis, and the median level of pleural fluid NT-proBNP was 1,741 pg/mL, while the serum NT-proBNP median level was 2,205 pg/mL.

Table 2. Etiologies of Pleural Effusion, According to Transudate or Exudate, Defined by the Criteria of Light et al[1]

	Transudate (no.)	Exudate (no.)
Malignant	0	22
Congestive heart failure	13	8
Parapneumonic	0	8
Empyema	0	7
Tuberculosis	0	5
Renal disease	1	1
Liver cirrhosis	1	0
Total	15	51

True transudates had a significantly higher serum-pleural fluid albumin difference (see Table 3). The serum-pleural fluid albumin difference > 1.2 g/dL had a sensitivity of 66.7%, a specificity of 67.6%, and positive and negative predictive values of 52.2% and 79.3%, respectively ($P = .02$), while a serum-pleural fluid protein difference > 3.1 g/dL had a sensitivity of 58.8%, a specificity of 81.8%, and positive and negative predictive values of 62.5% and 79.4%, respectively ($P = .02$) for discriminating transudates from exudates.

Receiver operating characteristic curve analysis (Fig. 3) demonstrated that an NT-proBNP cutoff value of $\geq$ 2,300 pg/mL in pleural fluid had a sensitivity of 70.8%, a specificity of 97.6%, and positive and negative predictive values of 94.4% and 85.4%, respectively ($P < .001$, diagnostic accuracy 87.9%) for discriminating heart-failure-related transudates from non-heart-failure-related pleural effusions. Table 4 gives detailed diagnostic information, including the appropriate decision statistics for the biochemical diagnosis of pleural effusions caused by heart failure. A pleural NT-proBNP cutoff value of $\geq$ 1,165 pg/mL in pleural fluid had a sensitivity of 95.8% for discriminating heart-failure-related effusions from exudates, with a specificity of 85.7%, and 8 of the 9 subjects misdiagnosed as exudates had pleural fluid NT-proBNP levels higher than 1,165 pg/mL.

Discussion

Our study showed that both plasma and pleural fluid NT-proBNP levels were significantly higher in subjects

Table 3. Pleural Fluid and Serum Parameters of True Transudates, True Exudates, and False Exudates

	True Transudates (n = 15)	False Exudates (n = 9)	True Exudates (n = 42)	P
Blood				
NT-proBNP, median (IQR), pg/mL	8,502 (5,357–25,625)	2,442 (1,206–3,339)	177 (72–631)	< .001
Protein, mean ± SD, g/dL	6.1 ± 1.6	7.1 ± 1.3	6.8 ± 0.9	.26
LDH, median (IQR), U/L	456 (287–604)	459 (380–497)	393 (283–535)	.51
Pleural				
NT-proBNP, median (IQR), pg/mL	11,620 (5,654–19,983)	2,024 (1,435–3,199)	367 (127–623)	< .001
Protein, mean ± SD, g/dL	2.2 ± 1.1	4.5 ± 1.8	4.3 ± 1.6	.003
LDH, median (IQR), U/L	161 (123–192)	360 (219–437)	472 (230–732)	.001
Pleural/Serum				
Protein ratio, mean ± SD	0.37 ± 0.12	0.66 ± 0.16	0.62 ± 0.20	.002
LDH ratio, mean ± SD	0.48 ± 0.32	0.79 ± 0.37	1.56 ± 1.39	.001
Albumin difference, mean ± SD, g/dL	2.36 ± 0.83	1.09 ± 0.71	1.12 ± 0.70	.001

LDH = lactate dehydrogenase
NT-proBNP = amino-terminal pro-brain natriuretic peptide

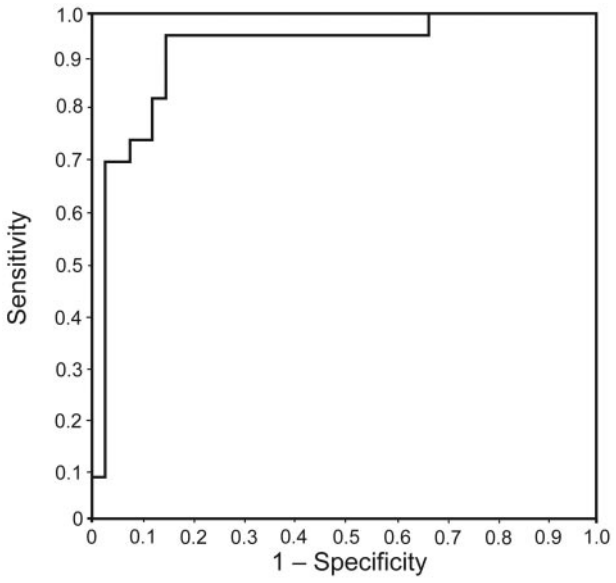

Fig. 3. Receiver operating characteristic curve of pleural fluid amino-terminal pro-brain natriuretic peptide (NT-proBNP) levels for differentiating true transudates from exudates. The area under the curve for pleural fluid NT-proBNP was 0.927 (95% CI 0.856–0.997).

with heart-failure-associated pleural effusion, compared to others. Our results were in accordance with the recent studies that explored the diagnostic value of BNP and NT-proBNP in the etiology of pleural effusions.[2,15–20] Han et al[2] measured pleural fluid and serum NT-proBNP levels in a consecutive series of 98 patients with heart failure and in 142 patients with other causes, and found that pleural fluid NT-proBNP levels among the heart-failure patients were significantly higher than others. Similarly, Porcel et al[18] retrospectively examined 117 patients with pleural effusion and found that the pleural fluid levels of NT-proBNP were significantly higher in patients with cardiac transudates than in patients with effusion of other causes. Tomcsányi et al[15] measured NT-proBNP levels in the pleural effusion of 14 patients with heart failure and 14 patients with different pleural pathology and found that heart-failure patients had significantly higher levels of NT-proBNP.

The pleural fluid NT-proBNP or BNP cutoff values for discriminating pleural effusion with heart failure vary from 1,176 pg/mL to 4,000 pg/mL.[7–11,13,14] Porcel et al[18] found that pleural fluid NT-proBNP level > 1,500 pg/mL predicted pleural effusion associated with heart failure with 91% sensitivity and 93% specificity. Han et al[2] reported that the pleural fluid NT-proBNP concentration of 1,714 pg/mL had a good accuracy (with 99% sensitivity and 99% specificity) for detecting heart-failure-associated transudate. Liao et al[14] showed that the pleural fluid NT-proBNP level of ≥ 2,220 pg/mL demonstrated a sensitivity of 100% and a specificity of 96.7% for the identification of heart failure. In our study we found that pleural fluid NT-proBNP level ≥ 2,300 pg/mL discriminated transudates caused by heart failure from exudates with 70.8% sensitivity and 97.6% specificity.

Tomcsányi et al[15] showed that the criteria of Light et al[1] had a sensitivity of 93% and specificity of 43% for transudates. However, the pleural fluid NT-proBNP accurately differentiated between the 2 groups. Han et al[2] reported that 28 patients with pleural effusion due to heart failure were misclassified as exudates by the criteria of Light et al,[1] and suggested that pleural fluid NT-proBNP levels identified 26 of them correctly. In our study 9 subjects out of 66 subjects (13.6%) were misdiagnosed as exudates according to the criteria of Light et al.[1] Pleural fluid NT-

Table 4. Diagnostic Information for Pleural Fluid NT-proBNP Concentration in the Diagnosis of Pleural Effusion Caused by Heart Failure

Pleural Fluid NT-proBNP Cut-off Values, pg/mL	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Diagnostic Accuracy (%)
1,165	95.8	85.7	79.3	97.3	89.4
1,704	83.3	88.1	80.0	90.2	86.4
2,000	75.0	92.9	85.7	86.7	86.4
2,300	70.8	97.6	94.4	85.4	87.9

NT-proBNP = amino-terminal pro-brain natriuretic peptide

proBNP levels of these 9 subjects were significantly higher than those of true exudates.

We preferred NT-proBNP measurement in our study. Porcel et al[18] compared the diagnostic accuracy of pleural fluid NT-proBNP and BNP levels for diagnosing pleural effusions due to heart failure. They found that the areas under the curve for NT-proBNP and BNP were 0.96 and 0.90, respectively, for diagnosing effusions due to heart failure. They also reported that age, sex, and serum creatinine level did not influence the NT-proBNP levels. They concluded that the pleural fluid NT-pro-BNP level was better than pleural BNP levels in establishing the diagnosis of heart-failure-associated effusions.

Diuretic treatment is a possible explanation for false exudates in heart-failure patients. Diuretics may change a transudate into an exudate by shifting fluid from the pleural space, which may elevate the levels of protein and LDH in the pleural fluid.[2–4,21] Pleural fluid NT-proBNP is suggested to be useful in the diagnosis of pleural effusion resulting from heart failure, especially in patients with exudates who are treated with diuretics. Han et al[2] reported that 26 of the 28 misclassified heart-failure patients received diuretics before thoracentesis and had pleural fluid NT-proBNP levels of higher than 1,714 pg/mL. In our study, 5 of the false exudates (55.6%) received diuretics before thoracentesis, and they all had pleural fluid NT-proBNP levels higher than 1,165 pg/mL.

We found a significant correlation between pleural fluid and serum NT-proBNP levels. Similarly, Han et al[2] reported that pleural fluid NT-proBNP levels were well correlated with serum NT-proBNP levels ($r = 0.93$, $P < .001$). The origin of NT-proBNP in pleural fluid is unclear. It has been suggested that it derives from serum NT-proBNP and might diffuse easily into the pleural space, due to its small molecular size.[22] Thus, some authors suggest the use of plasma BNP concentrations as a diagnostic tool for determining the cardiac etiology of pleural effusions[19] and note that there seems to be no additional value in measuring NT-proBNP in pleural fluid.[17] Actually, a high serum NT-proBNP level may even eliminate the need for diagnostic thoracentesis. But if a diagnostic thoracentesis is eventually to be done, pleural NT-proBNP may be measured alone, to confirm the diagnosis of heart-failure-associated pleural fluids.

Study Limitations

Our study has several potential limitations. First, this study was intended as a pilot study of using NT-proBNP in the diagnosis of pleural effusions. As a result, we limited our study population to patients with well defined causes of pleural effusion, thus excluding those in whom a definitive diagnosis could not be established. This design may somewhat cause overestimation of the receiver operating characteristic curves, but it is the first step in proving the validity of a diagnostic test. Additionally, we also excluded patients with effusions due to multiple etiologies. Heart failure is a frequent comorbidity in patients with pleural effusion, and it is essential to establish its role in pleural effusion. A future study with the inclusion of patients with effusions of multiple comorbidities may elucidate the diagnostic use of NT-proBNP in determining the role of heart failure in these patients. Second, given the limitations of low enrollment, we are currently not able to demonstrate to what extent pleural NT-proBNP concentration adds diagnostic information to the treating clinician's initial clinical impression. Finally, our study sample was limited in size and we could not adjust NT-proBNP concentrations, which were shown to be influenced by several factors, including age, sex, renal function, anemia, and obesity.[23,24] Plasma concentrations of NT-proBNP are higher in elderly patients, females, and in patients with renal failure. However, in the study of Porcel et al[18] age, sex, and serum creatinine level were not shown to influence the NT-proBNP levels. We believe that confirmation of our results and similar other studies in larger trials will yield accurate cutoff values for pleural NT-proBNP, and the simple test of pleural NT-proBNP determination may be routinely used in the differential diagnosis of pleural effusions.

Conclusions

NT-proBNP seems to be a reliable and accurate biomarker to diagnose patients with pleural effusion caused

by heart failure. The inclusion of pleural fluid NT-proBNP measurement in the routine diagnostic panel may enhance discrimination among the different causes of pleural effusions. The test may be useful in differentiation of heart-failure-related pleural effusions, especially in patients who have been treated with diuretics, and in this setting the pleural fluid NT-proBNP may be superior to the criteria of Light et al[1] for discriminating heart-failure-related effusions.

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