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EVALUATION OF EFFICACY OF PLEURAL FLUID NT-PROBNP IN DIFFERENTIATING PLEURAL EFFUSION DUE TO CARDIAC FAILURE FROM PLEURAL EFFUSION OF NON-CARDIAC ORIGIN

Cardiology

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ABSTRACT

Background: Light's criteria is used to distinguish an exudative pleural effusion from a transudative pleural effusion. These criteria have limitations in heart failure patients taking diuretics as they mis-classify cardiogenic pleural effusion as exudative. Serum NT-Pro BNP is an established marker of cardiac failure. In the search for an ideal biomarker for cardiogenic pleural effusion we conducted a prospective observational study to determine the efficacy of measuring pleural fluid NT-Pro BNP in differentiating cardiogenic pleural effusion from non-cardiogenic pleural effusion. **Methodology:** Ultrasound guided thoracocentesis was performed on 93 consented adults and pleural fluid aspirated along with serum samples were sent for examination. Samples were analysed for NT-pro BNP along with routine investigations performed in patients with pleural effusion to determine the etiology. Radiological investigations were performed including echocardiography to determine cardiac function. Pleural fluid NT-pro BNP in patients with clinico-radiological diagnosis of heart failure was compared to that of patients with non-cardiogenic pleural effusion. **Results:** Median pleural fluid NT-Pro BNP in cardiogenic pleural effusion was 11054 pg/ml which was significantly higher as compared to non-cardiogenic pleural effusion of 152 pg/ml. Area under the ROC curve showed that pleural fluid NT-Pro BNP was outstanding in predicting cardiogenic pleural effusion. At a cut off value of pleural fluid NT-ProBNP > 1459pg/ml the sensitivity was 100% and specificity was also 100% for predicting cardiogenic pleural effusion. 7 cases initially mis-classified as exudative pleural effusion were later correctly classified by elevated pleural fluid NT-Pro BNP as cardiogenic pleural effusion. **Conclusion:** Pleural fluid NT-Pro BNP is useful in discriminative diagnosis of cardiogenic pleural effusion and can be used to correctly identify mis-classified cardiogenic pleural effusion.

KEYWORDS

Pleural Effusion, Light's criteria, NT- ProBNP

INTRODUCTION

Pleural fluid is classified as a transudate or an exudate, which helps in determining the cause of pleural effusions. The differentiation of pleural effusion resulting from heart failure from those due to other causes is made clinically and radiologically, supported by the findings of a transudative effusion according to the Light's criteria.[1] This criteria has limitations in patients with heart failure and especially those who are taking diuretics. Some studies have found a considerable proportion of patients with pleural effusion due to heart failure being misclassified as exudative effusion.[2,3] Misdiagnosis of transudates as exudates may lead to unwarranted invasive interventions and may delay the initiation of appropriate therapy.

Several methods have been proposed to differentiate exudates from transudates, including the serum-effusion albumin difference, [4] serum-effusion protein difference, pleural cholesterol concentration [7] and pleural effusion/serum bilirubin ratio.[5] However, controversy exist as to which method is more accurate and effective.

The synthesis of vasoactive peptides is stimulated by increased tension or stretching of the cardiac ventricle wall. NT-pro-BNP measured in serum is a sensitive marker of cardiac dysfunction and has proven to be a useful tool in the diagnosis of acute and chronic systolic and diastolic left ventricular heart failure.[6]

Some recent studies have found pleural fluid NT-pro-BNP concentrations valuable in the discriminative diagnosis of pleural effusion related with cardiac disorders. Hence, in the search for an ideal biomarker for cardiac failure we wanted to evaluate the efficacy of pleural fluid NT-pro-BNP in differentiating pleural effusion due to heart failure from pleural effusion caused by non-cardiac causes.

METHODS

The study was conducted on 93 adult consented patients of both sexes after obtaining clearance from the ethical committee of the institution. Patient with radiologically determined pleural effusion that could be drained by thoracocentesis were included in the study. Patients with renal failure, coagulopathy, thoracic deformity interfering with thoracocentesis, effusion with more than one cause, hemothorax, chylothorax, urinothorax were excluded from our study.

Pleural fluid and serum samples were obtained from each subject. Pleural fluid was collected in the ethylenediaminetetraacetic acid (EDTA) tube by ultrasound guided thoracocentesis and serum samples were collected by venipuncture in EDTA tubes. Biochemical analysis, bacterial culture, acid-fast bacilli smear, polymerase chain reaction test for mycobacterium tuberculosis, ADA (adenosine deaminase) and cytologic examinations were performed on all pleural fluid samples, whereas serum samples were sent for biochemical analysis. Serum & pleural fluid total protein, lactate dehydrogenase (LDH) were measured using standard methods. Measurement of NT-pro BNP levels and all other biochemical analyses were carried out within 4 hours of specimen collection. NT-pro BNP levels were measured by chemiluminescence technique using VITROS ECi/ECiQ Immunodiagnostic system according to the manufacturer's protocol.
Chest x-ray and electrocardiography were obtained along with echocardiographic examination to determine biventricular systolic and diastolic functions, together with pulmonary hypertension and pericardial effusion, if present.

Data Collection

The demographic parameters and co-morbidities of the subjects were noted. The diagnosis of heart failure was based on the presence of symptoms and signs of cardiac failure & was confirmed by echocardiography, electrocardiography and chest x-ray. Pleural effusions were categorized as either exudative or transudative, according to the Light's criteria. Pleural effusions was diagnosed as malignant if malignant cells were detected on the cytologic examination of pleural fluid. Parapneumonic pleural effusion and empyema was diagnosed based on clinical and radiological findings of pneumonia or positive bacterial culture in pleural fluid. 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 granulomas were found in pleural biopsy, or when an exudative lymphocytic effusion with high adenosine deaminase levels (40 U/L) was present.

Statistical analysis was done with the use of Statistical Package for Social Sciences (SPSS) version 25. The association of qualitative variables were analysed using Chi-Square test. The comparison of quantitative variables were analysed using Mann-Whitney Test. Inter-rater kappa agreement was used to find strength of agreement between nature of fluid and diagnosis. Receiver operating characteristic (ROC) curve was used to find out cut off values of pleural fluid NT-Pro BNP

for predicting cardiogenic pleural effusion. Sensitivity, specificity, positive predictive value and negative predictive value were calculated. P value of less than 0.05 was considered statistically significant.

RESULTS AND OBSERVATIONS

79 (84.95%) patients belonged to age group 51-60 years. Age group was 61-70 years in only 14 out of 93 patients (15.05%).The mean value of age (years) of study subjects was 56.62 ± 5 with median (25th-75th percentile) of 56 (53-58).

Age(years)	Frequency	Percentage
51-60	79	84.95%
61-70	14	15.05%
Mean ± SD	56.62 ± 5	
Median(25^{th}-75^{th} percentile)	56(53-58)	
Range	51-70	

50 (53.76%) patients were females and 43 (46.24%) patients were males.

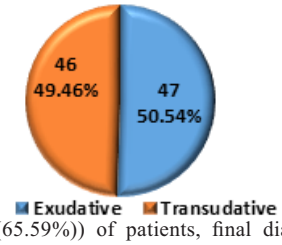
Gender	Frequency	Percentage
Female	50	53.76%
Male	43	46.24%
Total	93	100.00%

Mean value of body weight (kg) of study subjects was 65.24 ± 3.26 with median (25^{th}-75^{th} percentile) of 65 (63-68)

Variable	Mean ± SD	Median(25^{th}-75^{th} percentile)	Range
Body weight (kg)	65.24 ± 3.26	65(63-68)	54-77

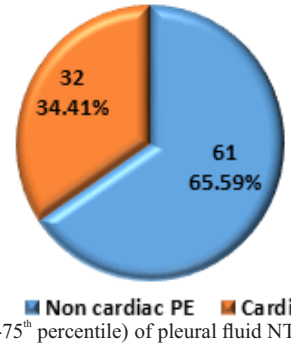
As per Light's criteria in majority (47(50.54%)) of patients, nature of fluid was exudative. Nature of fluid was transudative in 46 out of 93 patients (49.46%).

Distribution of nature of fluid of study subjects



In majority (61(65.59%)) of patients, final diagnosis was non cardiogenic pleural effusion (PE). The diagnosis was cardiogenic pleural effusion (PE) in 32 out of 93 patients (34.41%).

Distribution of diagnosis of study subjects



Median (25^{th}-75^{th} percentile) of pleural fluid NT-Pro BNP (pg/mL) in cardiogenic pleural effusion was 11054 (9743-13107) which was significantly higher as compared to non-cardiogenic pleural effusion of 152 (128-1100)). (p value <.0001)

Comparison Of Pleural Fluid NT-Pro BNP (pg/mL) Between Cardiogenic Pleural Effusion And Non Cardiogenic Pleural Effusion

Pleural fluid NT-Pro BNP (pg/mL)	Non Cardiogenic pleural effusion (n=61)	Cardiogenic pleural effusion (n=32)	Total	P value
Mean ± SD	490.39 ± 492	11555.5 ± 2103.79	4297.74 ± 5438.97	<.0001‡
Median(25^{th}-75^{th} percentile)	152 (128-1100)	11054 (9743-13107)	1100 (145-9767)	
Range	98-1459	9140-15908	98-15908	

All the parameters had significant discriminatory power to predict cardiogenic pleural effusion. Interpretation of the area under the ROC curve showed that the performance of pleural fluid NT-Pro BNP (pg/mL) (AUC 1; 95% CI: 0.961 to 1.000) was outstanding in prediction of cardiogenic pleural effusion. At a cut off value of pleural fluid NT-ProBNP > 1459pg/ml the sensitivity and specificity of pleural fluid NT-Pro BNP (pg/mL) was maximum; sensitivity 100% (89.1 - 100.0%) and specificity 100% (94.1 - 100.0%) for predicting cardiogenic pleural effusion. Pleural fluid NT-ProBNP had 100% positive predictive value & negative predictive value in distinguishing cardiogenic pleural effusion from non-cardiogenic pleural effusion.

Receiver Operating Characteristic Curve Of Pleural Fluid NT-Pro BNP (pg/mL) For Predicting Cardiogenic Pleural Effusion

Variables	Pleural fluid NT-Pro BNP (pg/mL)
Area under the ROC curve (AUC)	1
Standard Error	0
95% Confidence interval	0.961 to 1.000
P value	<0.0001
Cut off	>1459
Sensitivity(95% CI)	100%(89.1 - 100.0%)
Specificity(95% CI)	100%(94.1 - 100.0%)
PPV(95% CI)	100%(89.1 - 100.0%)
NPV(95% CI)	100%(94.1 - 100.0%)
Diagnostic accuracy	100.00%

7 out of 93 cases of pleural effusion were initially mis-classified as exudative pleural effusion by using the Light's criteria, but they were later correctly classified by elevated pleural fluid NT-Pro BNP as transudative effusion of cardiogenic origin.

Distribution Of Misclassified Cardiogenic Pleural Effusions Correctly Classified By Pleural Fluid NT-Pro BNP

Variables	Frequency	Percentage
Misclassified cases	7	7.53%
Total	93	100.00%

Mean value of pleural fluid NT-Pro BNP (pg/mL) in the initially misclassified pleural effusion of cardiogenic origin was 11279.43 ± 2085.6 with median (25th-75th percentile) of 11302 (9618-12094.5) which was similar to pleural fluid NT-Pro BNP (pg/mL) in cardiogenic pleural effusion 11054(9743-13107).

Descriptive Statistics Of Pleural Fluid NT-Pro BNP (pg/mL) In The Misclassified Pleural Effusion Of Study Subjects

Variable	Mean ± SD	Median (25^{th}-75^{th} percentile)	Range
Pleural fluid NT-Pro BNP (pg/mL) in the misclassified pleural effusion	11279.43 ± 2085.6	11302 (9618-12094.5)	9140-15089

DISCUSSION

The pleural fluid from a patient with heart failure is usually a transudate, as defined by the Light's criteria.[7] The main problem with these criteria is that they misidentify about 20 to 25% of transudates as exudates, especially after having received diuretic therapy.[8]

The serum NT-proBNP level is an established marker for the assessment of cardiac function, and has successfully been used as a tool for the diagnosis and management of acute and chronic heart failure, including systolic and diastolic left ventricular dysfunction and valvular disease. Pleural fluid NT-proBNP has been suggested to derive from serum NT-proBNP which can diffuse into the pleural space.[9]

The diagnostic value of the NT-proBNP concentrations in pleural fluid has been evaluated and increased levels of NT-proBNP in the pleural fluid have been observed in pleural effusions related with cardiac disorders. Hence on the basis of these studies we measured NTProBNP in pleural fluid to see whether it has a role in the discriminative diagnosis of pleural effusions related to cardiac failure.

We observed that the median pleural fluid NT-Pro BNP (pg/mL) in cardiogenic pleural effusion was 11054 (9743-13107) which was

significantly higher than the median pleural fluid NT-Pro BNP of non-cardiogenic pleural effusion that is 152 (128-1100). The p value was <0.0001. Our findings concurred with the findings observed by Porcel et al [10,11,12] who in three different studies reported that median NT-pro-BNP levels were significantly higher in pleural effusions related to cardiac failure than pleural effusions related to other causes. **Han CH et al** [13], **Mohamed E. Abdalla et al** [14] also noted that pleural fluid NT-proBNP levels were significantly higher in patients with cardiogenic pleural effusions than that of patients with non-cardiogenic pleural effusion.

Interpretation of the area under the ROC curve showed that the performance of pleural fluid NT-Pro BNP (AUC 1; 95% CI: 0.961 to 1.000) was outstanding in prediction of cardiogenic pleural effusion. At a cut off value of pleural fluid NT-ProBNP of > 1459pg/ml the sensitivity and specificity of pleural fluid NT-Pro BNP (pg/mL) was maximum; sensitivity 100% (89.1 - 100.0%) and specificity 100% (94.1 - 100.0%) for predicting cardiogenic pleural effusion. These observations were similar to observations made in a study conducted by **Porcel et al** [10] who noted that the cutoff value for the diagnosis of pleural effusions related to cardiac failure was 1300 pg/mL. The ROC analysis showed that sensitivity was 93.3%, specificity was 89.9%, and the area under ROC curve as 0.96. Similar observations were made by **Han CH et al** [13] who observed that at a cut-off point of > 1714 pg/ml, the pleural fluid NT-ProBNP had a sensitivity & specificity of 99% for diagnosis of heart failure. **Mohamed E. Abdalla et al** [14] also observed that at a cut-off value of 1591 pg/ml for pleural fluid NT-proBNP level the sensitivity was 95% and the specificity was 90% in the diagnosis of cardiogenic pleural effusion.

We observed that 7 (7.53%) out of 93 cases of pleural effusion were initially mis-classified as exudative pleural effusion. All these 7 cases, clinically and radiologically attributed to cardiogenic etiology had elevated pleural fluid NT-Pro BNP and hence got correctedly classified as transudative effusion of cardiogenic origin. We observed that the mean value of pleural fluid NT-Pro BNP (pg/mL) in the misclassified pleural effusion of study subjects was 11279.43 ± 2085.6 with median of 11302 (9618-12094.5) which was of similar range as cardiogenic pleural effusion.Our findings concurred with the observations made by **Han CH et al** [13] who observed that 28 patients with pleural effusion due to heart failure were initially misclassified as exudates by Light's criteria probably due to early administration of diuretics; 26 of them exhibited pleural fluid NT-proBNP levels of > 1714 pg/ml. Similar observations were made by **Bayram M et al** [15] who found that all the patients with pleural effusions who were misclassified as exudative by Light's criteria were correctly classified as transudative effusions by raised pleural fluid NT-proBNP. Similar observations were made by **Cincin A et al** [16], who noted that some patients with heart-failure were misclassified as exudates by Light's criteria, due to administration of diuretics before thoracentesis. All these misclassified patients had high pleural NT-proBNP levels which helped in identifying heart-failure-associated transudates.

CONCLUSION

We conclude that the median pleural fluid NT-Pro BNP in cardiogenic pleural effusion is significantly higher as compared to that of non-cardiogenic pleural effusion. At a cut off value of pleural fluid NT-ProBNP > 1459pg/ml the sensitivity is 100% (89.1 - 100.0%) and the specificity is 100% (94.1 - 100.0%) for predicting cardiogenic pleural effusion. Pleural fluid NT-ProBNP is efficacious in correctly identifying the mis-classified pleural effusions of cardiogenic origin by Light's criteria.

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