Comparison of serum & pleural levels of NT-ProBNP in patients with acute dyspnea and pleural fluid referred to Emergency Department

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Abstract: Pleural effusion is one of the most common manifestations of cardiac and non cardiac disease all over the world. The first step in the evaluation of patients with pleural effusion is to determine whether the effusion is a transudate or an exudate, that diagnostic Light criteria have been widely used. Although, this criteria are sensitive for identifying exudates, but they misclassify 15% to 25% of transudate as exudates. N-terminal B-type Natriuretic Peptide(NT-proBNP) is a cardiac neurohormone specifically secreted from the ventricles in response to volume expansion and pressure overload. This study aims at Comparison of serum and pleural levels of NT-ProBNP in patients with acute dyspnea and pleural fluid referred to Emergency Department and evaluating diagnostic value of serum and pleural NT-ProBNP in diagnosis of heart failure. In an analytic-descriptive cross-sectional study, 43 patients with acute dyspnea and pleural fluid in two groups (15 patients with CHF and 28 patients with other pathology) were analyzed in a 17 month period in Tabriz Emam Reza hospital. Samples of pleural fluid and serum were obtained from all patients on admission and NT-ProBNP was performed by electrochemiluminiscence immunoassay method. Also other biochemical analysis (albumin, total protein, cholesterol, triglyceride, amylase, LDH) were performed and gradient and ratio of this markers were accounted. The Mean ± SD serum NT-proBNP levels in CHF and non CHF patients were 15423 ± 3351 *pg/ml* and 4751 ± 1616 *pg/ml*, respectively; and plural NT-ProBNP levels in CHF and non CHF patients were 14822 ± 3249 *pg/ml* and 3569 ± 1231 *pg/ml*, respectively. Using a cut-off value of 2350 *pg/mL* for serum and 1750 *pg/ml* for pleural samples, the accuracy of NT-proBNP for identifying pleural effusions from cardiac causes was 76%, the sensitivity and specificity was 93.3% and 76.9%, respectively; The positive and negative likelihood ratio was 3 and 0.10 , respectively. The positive and negative predictive value was 60% and 95%, respectively. In this study Light criteria had 40% sensitivity and 78% specificity in identifying cardiac causes of pleural effusion. NT-proBNP is better than Light's criteria and a useful marker for the diagnosis of pleural effusions from heart failure when measured in either serum or pleural fluid.

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1. Introduction

Pleural effusion is one the most common presentations of both cardiac non cardiac diseases (Light, 2002). Heart failure, malignancies, pneumonia, tuberculosis and pulmonary embolism are most common causes of pleural effusion in adults(Porcel and Light, 2006). Determining that the pleural fluid is transudative or exudative is the first step in evaluating the patients with pleural effusion and finally making the diagnosis which mainly is made by Light's criterias (Porcel, 2011) but in 15 to 25% of cases this leads to misclassification (Porcel, 2006).

Burgess et al, have used Albumin gradient and Caderia et al have used Protein gradient >3.1 for determining the type of pleural effusion. Despite the use of both gradients, 10% of exudates are still misclassified as exudates. NT-proBNP measurement is one of the proven methods for diagnosis of heart failure in people with acute dyspnea referring to emergency department. NT-proBNP is a cardiac neurohormone secreting from cardiac ventricles in response to increase of volume and overload of cardiac ventricles (Porcel, 2007).

Some studies have stated that a cut off value of serum and pleural fluid NT-proBNP levels is not equal in patients with heart failure in all ages and all races (Raymond, 2003). Considering the importance and emphasizing the differences in cut off values for age, race, sex, diseases and ... It seems that these numbers need to be reviewed for Iranian with considering the other indicators. Our aim of this

study is to evaluate the diagnostic value of serum NT-proBNP in the diagnosis of heart failure in addition to recommend a Cut off number with regard to the number of known cases to take an effective step in quick and easy diagnosis of heart failure and the approach to this disease especially in emergency room.

2. Material and Methods

In a cross sectional descriptive-analytic study on patients with acute dyspnea and pleural effusion in emergency department of Tabriz Imam Reza Hospital the diagnostic value of serum NT-proBNP in the diagnosis of heart failure were studied. 43 patients with acute dyspnea who had pleural effusion on chest radiograph were enrolled to the study,15 of them had a pleural effusion due to heart failure (group A) and 28 of them were classified with pleural effusion with non cardiac causes(group B). Non-cardiac causes were included pulmonary thromboembolism, cancer, parapneumonic effusion, nephrotic syndrome, cirrhosis and had Chronic Myelogenous Leukemia with extramedullary hematopoiesis. After assessing of patients, clinical diagnosis of pleural effusion was established, without the knowledge of the laboratory results. Then with gathering of laboratory, echocardiographic and pathologic findings patients were classified as group A if they had cardiac pleural effusion and otherwise they were classified as group B.

The diagnoses of heart failure in patients were made according to Framingham, echocardiography and American college of cardiology criterias. Other patients were followed up after admission in order to be enrolled upon their diagnosis. Of all patients with pleural effusion and acute dyspnea, and after providing necessary explanations for patients and their families regarding the goals and methods and after obtaining consent, 3 ml venous blood was taken and sent to the laboratory. Serum and pleural fluid samples were centrifuged at 4 ° C and were examined.

Measurement of NT-ProBNP levels in serum was done using the electrochemiluminiscence immunoassay method and results were recorded as Pico gram per Milliliter (*pg/ml*). In this study, NT-proBNP in addition to several other diagnostic markers in pleural fluid and blood were examined simultaneously, including Glucose, albumin, total protein, and lactate dehydrogenase, cholesterol, Triglyceride, WBC count, respectively.

Exclusion criteria included patients with acute coronary syndrome, septic shock, and atrial fibrillation with rapid ventricular response.

Ethical considerations:

Informed consent for thoracentesis and blood sampling were obtained from all patients, regulations of ethical considerations related to the Medical University of Tabriz**,** was observed in all patients. This study has been approved by the Ethical Committee of Tabriz University of Medical Sciences.

Statistical Analysis:

We used descriptive analytical test (Mean ± SD), frequency and percentage for presenting descriptive data to compare qualitative data. Chi-square test or Fisher's exact test was used. We also evaluated the normal distribution of laboratory data for studying their mean difference and due to their lack of normal distribution we used Non parametric u-Mann Whitney test. For studying the Relationship between serum and pleural fluid NT-proBNP Spearman test was used and we used ROC curve (Receiver operating characteristic curve) for determining the Cut off point for NT-ProBNP to diagnosing heart failure. In all cases, P-value less than 0.05 was considered significant.

3. Results

In this study 43 patients with acute dyspnea and pleural effusion assessed. 15 patients in Group A (CHF) and 28 in Group B (Non CHF). Non CHF patients included PTE (Pulmonary Thromboembolism), Cancer, Parapneumonic effusion, Nephrotic syndrome, Cirrhosis and one case with extramedullary hematopoiesis. 28 patients (9 patients in group A, 19 patients in group B) were male and 15 patients (6 patients in group A, and9 patients in group B) were female (P=0.74).

There is no significant difference between 2 groups (A, B) in age, sex variables.

In addition NT-proBNP, other diagnostic markers (Glucose, Albumin, Total protein, lactate dehydrogenase, cholesterol, Triglyceride, amylase, WBC count) in serum and pleural fluid were measured simultaneously and calculated their gradients and ratio (table 1 and 2). U-Mann Whitney test showed that only some variable [Plural Glucose (P=0.017) Plural WBC (P=0.012), Pleural/Serum Albumin (P=0.04), Serum-Pleural Albumin gradient (P=0.003), Serum-Pleural Protein gradient (P=0.003)] had significant deference between two groups. As regards plural Glucose affected with elevated serum glucose in diabetic patients, there is
Based on recent recommended criteria 8 (53.3%) cases in Group A and 8 (28.5%) cases in Group B classified as transudate. No significant difference between 10 heart failure patients and 22 patients with non cardiac causes of pleural effusion, after exclusion of diabetic patients.

Table 1. Serum and Pleural Fluid guardian analysis based on pleural effusion type and patients diagnosis

		Transudative (n±16)	Exudative (n±27)	P	Cardiac (n±15)	Non Cardiac (n±28)	P
Serum	Blood glucose	1.02 ± 0.33	0.83 ± 0.33	<0.001	0.98 ± 0.32	0.86 ± 0.35	0.23
	Albumin	0.38 ± 0.12	0.71 ± 0.17	<0.001	0.49 ± 0.15	0.64 ± 0.24	0.04
	Pr	0.37 ± 0.09	0.65 ± 0.18	<0.001	0.45 ± 0.12	0.60 ± 0.22	0.017
	LDH	0.30 ± 0.15	1.06 ± 0.31	<0.001	0.87 ± 0.53	0.73 ± 0.14	0.05
	Chool	0.26 ± 0.18	0.49 ± 0.18	0.94	0.36 ± 0.22	0.43 ± 0.20	0.12
	TG	0.24 ± 0.09	0.20 ± 0.05	0.08	0.27 ± 0.12	0.19 ± 0.04	0.33
	Amylase	0.62 ± 0.27	1.5 ± 0.73	0.001	0.78 ± 0.12	1.4 ± 0.7	0.74
	NT-proBN	0.72 ± 0.10	1.4 ± 0.34	0.12	0.98 ± 0.35	1.2 ± 0.34	0.98
Pleural Fluid	Blood glucose	0.43 ± 8.7	32 ± 13	<0.001	12 ± 14	25 ± 11	0.34
	Albumin	1.8 ± 0.45	0.95 ± 0.59	<0.001	1.7 ± 0.59	1.06 ± 0.64	0.003
	Pr	3.8 ± 0.59	2.1 ± 1.2	0.055	3.5 ± 0.87	2.3 ± 1.3	0.003
	LDH	621 ± 81	246 ± 213	0.063	527 ± 332	310 ± 123	0.18
	Chool	131 ± 84	85 ± 50	0.14	117 ± 65	94 ± 69	0.27
	TG	74 ± 18	100 ± 18	0.27	69 ± 17	102 ± 18	0.56
	Amylase	23 ± 4	13 ± 31	0.01	18 ± 7	9 ± 29	0.42
	NT-proBN	2505 ± 856	75 ± 417	<0.001	600 ± 877	1182 ± 505	0.95

Table 2. Serum and Pleural Fluid analysis based on pleural effusion type and patients diagnosis

		Transudative (n±16)	Exudative (n±27)	P	Cardiac (n±15)	Non Cardiac (n±28)	P
Serum	Blood glucose	118 ± 49	151 ± 72	0.085	164 ± 37	125 ± 50	0.066
	Albumin	3.1 ± 0.8	3.3 ± 0.5	0.33	3.4 ± 0.5	3.2 ± 0.7	0.48
	Pr	6.1 ± 0.9	6.3 ± 0.7	0.61	6.5 ± 0.6	6.1 ± 0.9	0.24
	LDH	876 ± 77	1117 ± 58	0.45	1092 ± 189	993 ± 126	0.89
	Chool	172 ± 76	163 ± 50	0.94	176 ± 48	161 ± 66	0.20
	TG	95 ± 72	126 ± 92	0.11	107 ± 12	119 ± 29	0.71
	Amylase	57 ± 21	68 ± 34	0.48	68 ± 25	61 ± 33	0.13
	NT-proBN	13905 ± 3527	5255 ± 1561	0.017	15423 ± 3351	4751 ± 1616	<0.001
Pleural Fluid	Blood glucose	118 ± 53	119 ± 68	0.75	152 ± 71	100 ± 49	0.017
	Albumin	1.2 ± 0.5	2.4 ± 0.7	<0.001	1.6 ± 0.4	2.1 ± 0.9	0.10
	Pr	2.3 ± 0.7	4.2 ± 1.4	<0.001	2.9 ± 0.8	3.8 ± 1.7	0.0900
	LDH	254 ± 39	871 ± 177	<0.001	565 ± 241	683 ± 137	0.18
	Chool	41 ± 36	77 ± 32	<0.001	58 ± 10	67 ± 7	0.27
	TG	20 ± 12	25 ± 9	0.10	38 ± 20	16 ± 3	0.25
	Amylase	33 ± 28	81 ± 30	0.025	50 ± 7	71 ± 29	0.34
	NT-proBN	11399 ± 3258	5180 ± 1591	0.10	14823 ± 3250	3569 ± 1231	0.066

Table 3. Serum and Pleural Fluid levels of NT-proBNP based on several diagnoses

	Cardiac Failure	PTE	Cancer	Parapunomic Pleural effusion
Serum	15423 ± 3351 (1348-35000)	7118 ± 4384 (60-27544)	1457 ± 951 (27-9832)	7260 ± 3875 (58-35000)
Pleural Fluid	14822 ± 3249 (1482-35000)	6104 ± 3378 (95-19907)	1035 ± 450 (206-4613)	5024 ± 2985 (6-25776)

Table 4. Diagnostic characteristic of Serum and Pleural Fluid levels of NT-proBNP in two different cut of points

	Cut off point (pg/ml)	Sensitivity	Specificity	PPV	NPV	Positive Likelihood Ratio	Negative Likelihood Ratio	Diagnostic Accuracy	Odds Ratio
Serum	2378	93.3%	67.9%	60%	95%	3	0.10	76%	29.5
	6412	80%	78.6%	66%	88%	3.8	0.20	79%	14.6
Pleural Fluid	1759	93.3%	67.9%	60%	95%	3	0.10	76%	29.5
	2452	86.7%	75%	65%	91.3%	3.4	0.17	79%	19.5

In group A (CHF), only 6(40%) cases classified transudate based on Light's criteria and 9 cases (60%) classified as exudative fluids. Thus in our CHF patients, the Light's criteria had a sensitivity of 40% and specificity of 78% in diagnosing transudative pleural fluids due to CHF.

In our study pleural fluid labeled as transudative, if all of 3 following criteria was met:

1) Fluid/Serum Protein level < 0.5
2) Fluid/Serum LDH level < 0.6
3) Fluid and Serum Albumin gradient >1.2

The mean level of NT-proBNP in exudative effusions was 13905.49 ± 3527.86 *pg/ml* and in transudative effusions was 5255.82 ± 1560.44 *pg/ml*(P-value=0.017). The cut off point was determined 3331 *pg/ml* for serum NT-proBNP level to diagnosing transudative pleural fluid with a sensitivity of 75% and a specificity of 63% (Figure1). Mean levels of NT-proBNP in pleural fluids was 11399.92 ± 3185.41 *pg/ml* and in the exudative effusions was 5180.64 ± 1591.29 *pg/ml* (p=0.102).

Table 3 shows Serum and Pleural levels of NT-proBNP upon different diagnosis. There was a meaningful correlation between NT-proBNP serum (P=0.016) and pleural levels (P=0.008) in different diagnosis.

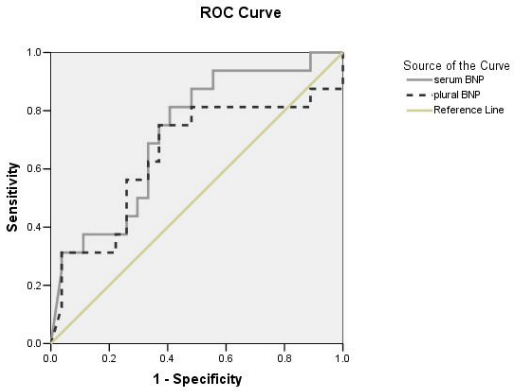

Figure 1. ROC chart of Serum and Pleural Fluid levels of NT-proBNP in diagnosis of transudative pleural effusion

Mean values of serum NT-Pro BNP was 15423.13 ± 3351.68 *pg/ml* in Group A and 4751.72 ± 1616.95 *pg/ml* in Group B(P < 0.001).

Mean values of Pleural NT-Pro BNP was 14822.93 ± 3249.42 *pg/ml* in Group A and 3569.01 ± 1231.78 *pg/ml* in Group B(P-value < 0.001). These values calculated with U-Mann Whitney test, and then cut of values were calculated.

The cut off number for pleural and serum levels for Nt-proBNP was calculated with ROC curve. Area under the curve for serum NT-proBNP with P<0.001 and 95%CI: 0.71-0.95 was 83.6%.

Accuracy, sensitivity, specificity, positive and negative predictive value and positive and negative Likelihood Ratio to diagnose heart failure based on the Cut off point NT-proBNP serum & Pleural Fluid is shown in Table 4 (Figure 2).

9 out of 15 patients with heart failure (60%) who was classified as exudate was diagnosed correctly based on NT-proBNP (2378 serum and 1759 pleura), while only 5 patients (55%) based on albumin gradient, and 4 patients (44%) based on the protein gradient were classified correctly. With significant differences of some of the other variables between the two groups, the Cut off were calculated for each of the variables.

Albumin gradient between serum and pleural fluid with Cut off point =1.2 had a sensitivity of 73% and specificity of 57% and with a cut off point=1.45 had a sensitivity of 66.7% and a specificity of 75% for the diagnosis of heart failure.

Spearman's test showed that, there is a positive statistical correlation in all patients with pleural effusion and serum and pleural fluid NT-proBNP (r=0.92, P<0.001) (Figure 2).

We studied the serum and pleural levels of Nt-proBNP in patients with acute dyspnea and pleural effusion who had the indication of thoracentesis. Serum and pleural fluid Nt-proBNP levels was higher in patients with heart failure in comparison to other patients. In other word with the rise of Nt-proBNP levels in serum the NT-proBNP levels in pleural fluid will also increase. NT-proBNP in serum and pleural fluid can determine the type of pleural effusion more accurately than the Light's criteria and in cases which there is a misclassification of exudate or transudate nature of pleural effusion ,this marker can effectively identify the cause of pleural effusion particularly in cases with pleural effusion due to congestive heart failure.

In our study the lights criteria in diagnosing the pleural effusion due to CHF has a sensitivity of 40% and a specificity of 78% while NT-proBNP had a sensitivity of 93.35 and a specificity of 67.9% in diagnosing the pleural effusion due to cardiac causes with a cutoff point of 1759 *pg/ml* in pleural fluid and 2378 *pg/ml* in serum .In these values serum NT-ProBNP had a positive predictive value(PPV) of 60%, negative predictive value(NPV) of 95%, positive Likelihood ratio(+LR) of 3 and, negative Likelihood ratio(-LR) of 0.1 in identifying of CHF patients(Figure 3).

If we choose serum value of 6412 *pg/ml*, NT-ProBNP have a sensitivity of 80%, specificity of 78.6% , accuracy of 79%, PPV=66%, NPV=88%, (+LR)=3.8, (-LR)=0.2.

For Pleural fluid NT-ProBNP value equal to 1759 *pg/ml* a sensitivity of 93.3%, specificity of 67.9% , accuracy of 76%, PPV=60%, NPV=95%, (+LR)=3, (-LR)=0.1 in identifying CHF patients calculated.

If we choose pleural value of 2452 *pg/ml*, NT-ProBNP have a sensitivity of 86.7%, specificity of 75%, accuracy of 79%, PPV=65%, NPV=91.3%, (+LR) =3.4, (-LR) =0.17. Correlation between Serum and Pleural Fluid levels of NT-proBNP was shown if figure 4.

4. Discussions

In our study the mean serum level for in patients with heart failure was 15423 *pg/ml* and in non cardiac patients was 3569 *pg/ml*. serum NT-proBNP for diagnosing the heart failure has the highest sensitivity in cut off above 2378 *pg/ml* and highest specificity in cut off above 6412 *pg/ml*. Pleural NT-proBNP for diagnosing the heart failure has the highest sensitivity in cut off above 1759 *pg/ml* and highest specificity in cut off above 2452 *pg/ml*.

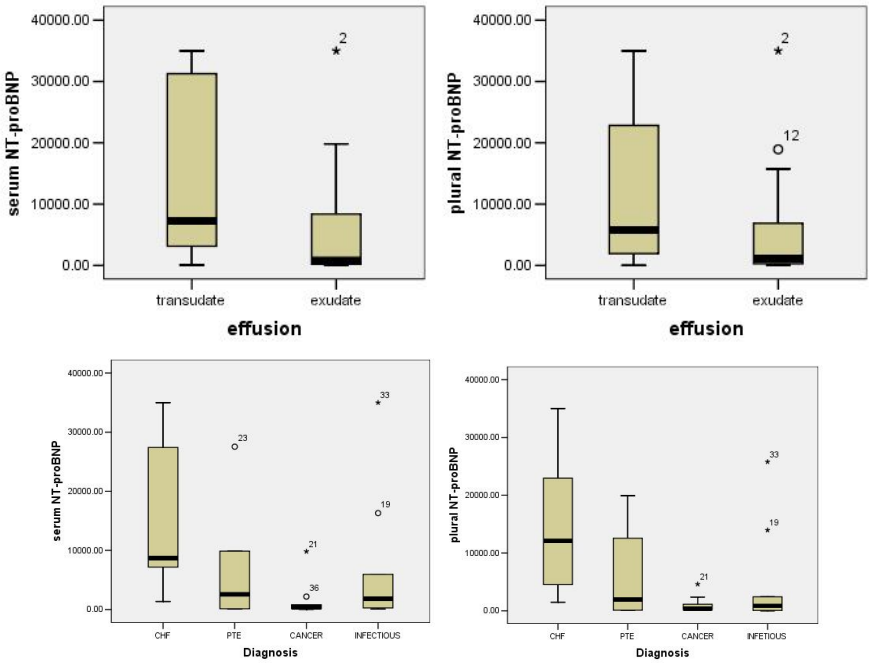

Figure 2. Comparing Serum and Pleural Fluid levels of NT-proBNP distribution in transudative or exudative pleural effusion

Roth BJ et al on their study showed that 28% of the CHF pleural effusions were misclassified using the Light's criteria as exudates (Roth, 1990).
Skouras and colleagues evaluated the diagnostic role of BNP in heart failure and stated that high ratios of pleural effusions in non-cardiac effusions is as an effect of increased permeability of the pleura, local production or reduced removal of pleural cavity as well as that of BNP levels can not differentiate the transudate or exudate of pleural effusion(Skouras, 2008).
In a study by Procel and colleagues on 93 patients (53 patients with heart failure and 40 non-cardiac patients), Cut off point = 1500 *pg/ml* for NT-proBNP in serum and pleural fluid with had an accuracy of 89% and 90% in detecting pleural effusions with cardiac causes. They stated that pleural fluid or serum NT-proBNP with cut off more than 1500 *pg/ml* is helpful in the diagnosing of heart failure (Porcel, 2007).
In a study by Kolditz and colleagues, NT-proBNP at a cut off of more than 4000 *pg/ml* in serum and pleural fluid has a sensitivity of 88% and 92% respectively a 92% and 93% specificity and diagnostic accuracy of 91% and 92%respectively in the diagnosis of heart failure. All patients who incorrectly classified as Light criteria in this study were correctly identified by measuring NT-proBNP (Kolditz, 2006).

Mueller and colleagues stated that most of the diagnostic accuracy of BNP for heart failure is at the cut off = 295 ng/l (*Pg/ml*) (sensitivity 80%, specificity 86%, positive predictive value and negative predictive value 78% with 87% accuracy 83%). The highest Diagnostic Accuracy for NT-proBNP was in cut off = 825 ng/l (*Pg/ml*) (sensitivity 87%, specificity 81%, positive predictive value and negative predictive value 84% with 84% accuracy% 84)they stated that BNP and NT-proBNP in patients with complaints of dyspnea can be very useful in helping to diagnose CHF (Mueller, 2005).
Tomcsanyi and colleagues investigated the role of NT-proBNP in distinguishing exudate or transudate nature of pleural fluid and stated that median level for pleural fluid NT-proBNP levels in patients with heart failure was 6295 *Pg/ml* and in non-cardiac patients 276 *Pg/ml*. it was significantly higher (P =0.0001)in patients with heart failure and found that pleural fluid NT-proBNP levels can distinguish the two groups with high accuracy, while the Light's criteria for transudative pleural fluid has a sensitivity of 93% and specificity of 43%. They suggested that entering the -level assessment of pleural NT-proBNP in routine diagnostic panels can increase the diagnostic power of the different causes of pleural effusions in patients with such disorder. (Tomcsányi, 2004).

Gegenhuber and colleagues stated that the sensitivity, specificity and diagnostic accuracy of BNP levels in the Cut off point = 520 *Pg/ml* for the diagnosis of pleural effusion due to heart disease is 97%, 89% and 93% and at the Cut off point = 2201 *Pg/ml* is 77%, 100% and 88% respectively (Gegenhuber, 2005).

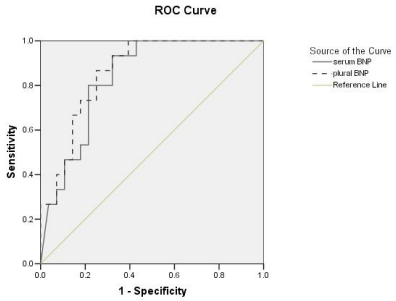

Figure 3. ROC chart of Serum and Pleural Fluid levels of NT-proBNP in diagnosis of heart failure

In systematic review conducted in 2010 by Surinder Janda and John Swiston assessing accuracy (diagnostic accuracy) the mean NT-proBNP levels in pleural fluid in effusion with cardiac origin was 6140 *pg/ml*. The average sensitivity and specificity of pleural fluid NT-proBNP in the total of the studies was % 94 (95%CI: 97-90) and% 94 (995%CI: 97-8) and mean levels of positive Likelihood Ratio was 15.2 (95%CI: 8.1-28.7) and negative Likelihood Ratio was 0.06 (95%CI: 0.03-0.11), respectively. Area under ROC curve was equal to 0.98 (95%CI: 0.98-0.99) and diagnostic odds ratio was equal to 246 (95%CI: 81 -745) respectively. They concluded that NT-proBNP a level of pleural fluid is a very useful biomarker with high diagnostic accuracy distinguishing pleural effusion is of cardiac origin (Janda, 2010).

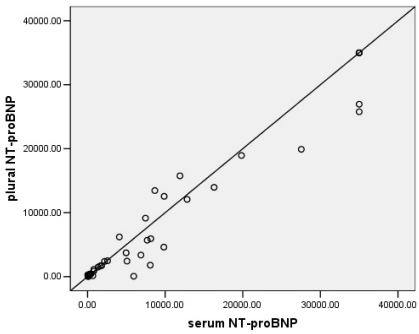

Figure 4. Correlation between Serum and Pleural Fluid levels of NT-proBNP

In the meta-analysis conducted by Zhou Q and colleagues in 2010 in China they stated that NT-proBNP in pleural fluid, had a sensitivity of 95% (95%CI: 97-92), specificity of 94% (95%CI: 96-92) positive Likelihood Ratio 14.12 (51/19-23/1095%CI:10.23-19-51) and negative Likelihood Ratio 0.06 (95%CI:0.04-0.09) and diagnostic odds ratio equal to 213 (95%CI:122-273)in diagnosing pleural effusion with cardiac origin (Zhou, 2010).

Recommendations:

According to the results of this study, NT-proBNP when is measured simultaneously in serum and pleural fluid can help in determining the cause of the effusion more than Light's criteria and it can be a simple and useful marker in detecting the cause of pleural effusion due to heart failure. Thus equipping emergency department's laboratories for the measurement of these markers can be an important and effective step in the diagnosis and determining the patient's illness.

Several cases to consider in future studies are recommended:

1) Conducting comparative studies with other diagnostic modalities in patients with dyspnea and pleural effusion.
2) Evaluating the prognosis of patients who were diagnosed and treated with this method
3) Evaluation of this marker in the diagnosis of pleural effusion with other important causes particularly pulmonary embolism

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