High diagnostic accuracy of NT-proBNP for cardiac origin of pleural effusions

Martin Kolditz¹, MD; Michael Halank¹, MD; C. Steffen Schiemanck¹, MD; Alexander Schmeisser², MD; Gert Höffken¹, MD

¹ Department of Pulmonology, Medical Clinic I, University Hospital Carl Gustav Carus, Dresden, Germany
² Department of Cardiology, Medical Clinic II, University of Technology Dresden, Germany

Corresponding author:
Martin Kolditz
Department of Pulmonology
Medical Clinic I
University Hospital Carl Gustav Carus
Fetscherstr. 74
01307 Dresden, Germany
Telephone: +49-351-4584538, FAX: +49-351-4585892
Email: martin.kolditz@uniklinikum-dresden.de

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Abstract:

A prospective study was performed to evaluate the diagnostic accuracy of NT-proBNP measured simultaneously in serum and pleural fluid to identify pleural effusions due to heart failure.

Pleural fluid and serum samples from all patients presenting for thoracentesis between April 2004 and May 2005 were simultaneously collected. The discriminative properties of NT-proBNP to identify pleural effusions due to heart failure were determined by ROC-curve analysis and compared to the diagnostic value of finding a transudate by Light’s criteria.

93 patients were evaluated, 27% with cardiac effusion and 73% with exudative effusions of various causes. Levels of NT-proBNP in pleural fluid and serum correlated closely. Serum and pleural fluid NT-proBNP was significantly elevated in patients with cardiac effusion. With a cut-off value of 4000 ng/l, NT-proBNP levels in pleural fluid and serum displayed comparably high diagnostic accuracies of 92% and 91%, respectively. All patients misclassified by Light’s criteria were correctly identified by measuring NT-proBNP.

NT-ProBNP levels in either pleural fluid or serum showed a high diagnostic accuracy when compared to the traditional criteria. Thus, measuring of NT-proBNP is a valuable additional diagnostic tool to detect or exclude cardiac origin of pleural effusions.
Key words:

B-type natriuretic peptide
Exudates and transudates
Heart failure
Pleural effusion
**Introduction:**

The differentiation of pleural effusions resulting from heart failure versus other causes is usually made by clinical criteria supported by the finding of a transudative effusion according to the criteria of Light (see Table 1) (1). However, as these criteria were developed to detect exudative pleural effusions with high sensitivity for not overseeing underlying causes like infections and malignancies, their ability to exclude transudative effusions is lower (1, 2). Some studies found a considerable proportion of patients with pleural effusions due to heart failure being misclassified as exudate (3, 4), especially after having received diuretic therapy (5). The finding of an exudative effusion usually requires an extensive diagnostic workup. Thus a diagnostic dilemma in patients with exudative pleural effusions and clinical heart failure might result, leading to an unnecessary exposure of invasive and expensive diagnostic procedures. On the other hand, thoracentesis itself possesses a considerable risk of complications and is associated with discomfort to the patient. Thus a strategy of identifying pleural effusions due to heart failure and possibly avoiding unnecessary diagnostic thoracenteses and / or further diagnostic procedures would be an attractive and potentially beneficial approach.

B-type natriuretic peptide (BNP) is a vasoactive peptide secreted predominately by the heart. Its precursor molecule proBNP is cleaved into the inactive N terminal proBNP (NT-proBNP) and the biologically active BNP. The synthesis of these peptides is stimulated by increased tension or stretching of the cardiac ventricle wall. NT-proBNP measured in serum is a sensitive marker of cardiac dysfunction and has been proved as a useful tool in the diagnosis of acute and chronic systolic and diastolic left ventricular heart failure (6, 7, 8, 9).

Recently there has been some interest in the investigation of these peptides as markers for pleural effusions due to heart failure. So far two studies examined NT-proBNP (10, 11) and one measured BNP (12), with all uniformly suggesting a potential value of these peptides in
predicting or ruling out heart failure as cause of pleural effusions. There are however several limitations to these trials as they either measured the peptides only in pleural fluid (11) or in plasma (12), were of retrospective design (11) or included only 28 selected patients to analyse (10).

The aim of this study was to prospectively evaluate the diagnostic accuracy of NT-proBNP, measured simultaneously in serum and pleural fluid, to identify pleural effusions due to heart failure in all patients presenting for thoracentesis in our clinic between April 2004 and May 2005.

**Methods:**

Pleural fluid and serum samples were collected prospectively from all patients presenting in our clinic in a tertiary care university hospital for diagnostic or therapeutic thoracentesis between April 2004 and May 2005. In patients presenting repeatedly for thoracentesis, only the first episode was included. Pleural fluid and serum samples were obtained preferably simultaneously, but a maximum time difference of +/- 8 hours was accepted. Biochemical analysis, bacterial and fungal culture, acid fast bacilli smear, Polymerase chain reaction for *Mycobacterium tuberculosis* complex DNA and cytological exams (with flow cytometry if appropriate) were performed in all pleural fluid samples shortly after thoracentesis, whereas serum samples were sent for biochemical analysis. Measurement of NT-proBNP in serum and pleural effusion and all other biochemical analyses were carried out within 4 hours after specimen collection.

Any further diagnostic workup was left to the discretion of the attending physicians, but echocardiography was performed in all patients with suspected pleural effusion due to heart failure.
The study protocol was approved by the local ethics committee, and informed consent was obtained from the participants.

Serum and pleural fluid total protein, lactate dehydrogenase (LDH) and cholesterol levels were measured using test kits from Roche Diagnostics GmbH (Mannheim, Germany) on the analyser Hitachi 917 (Roche Diagnostics GmbH, Mannheim, Germany). The upper normal limit for serum LDH with the used test kit is 213 U/l for women and 225 U/l for men. NT-proBNP was measured by electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturers protocol. According to the manufacturer this test has an intra-assay coefficient of variation of 0.8 to 3%, and a detection range from 5 ng/l to 35000 ng/l. Higher values were obtained by diluting samples 1:10 or 1:100.

After the termination of the study, when the last included patient had been discharged from hospital, clinical diagnosis was established independently from the biochemical data by reviewing the hospital records of all patients.

The diagnosis of heart failure was based on the findings of the typical clinical picture of decompensated heart failure, including history, physical examination, chest radiograph, and response to diuretic therapy, and confirmed by echocardiographic evidence of left ventricular systolic dysfunction (left ventricular ejection fraction ≤ 40%), severe valvular disease grade II or III, or severe left ventricular diastolic dysfunction; all patients with pleural effusions due to heart failure had New York Heart Association class III or IV symptoms.

Malignant effusions were diagnosed when malignant cells were detected on cytologic exam of pleural fluid or in lung biopsy specimens in the absence of other causes of pleural effusions.
Parapneumonic effusions or pleural empyemas were associated with the clinical and radiological diagnosis of acute pneumonia or the detection of pus or a positive bacterial culture in pleural fluid.

Other, rare causes of exudative pleural effusions were defined by clear clinical pictures or established diagnostic criteria (postcardiac injury syndrome, acute pleuritis, postoperative effusion, collagen disease, pleural tuberculosis, chylothorax).

Data of biochemical analyses including NT-proBNP are presented as median and 25th and 75th percentiles. Medians were compared using the non-parametric Mann-Whitney test and qualitative variables were compared using the Fisher exact test. The correlation between pleural fluid and serum NT-proBNP concentration was tested using the Spearman coefficient of rank correlation. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated according to standard formulas. The exact binominal 95% confidence intervals were calculated for all operational characteristics. Receiver operating characteristic (ROC) curve analysis was used to determine the discriminative properties of various cut-off levels of NT-proBNP. A p-value of <0.05 (two-sided) was considered statistically significant. Statistical analyses were performed with SPSS version 11.0 software (SPSS, Inc., Chicago, Illinois). The regression equation according to the Passing and Bablok method was calculated as described previously (13).

**Results:**

Pleural fluid and serum samples were collected from 101 consecutive patients presenting for thoracentesis in our clinic between April 2004 and May 2005. 8 patients (8%), in whom a definite diagnosis could not be established from the hospital records, were excluded from the
analysis. The remaining 93 patients divided into the following diagnoses according to the above mentioned criteria:

25 patients (27%) with effusions due to heart failure, 40 patients (43%) with malignant effusions, 15 patients (16%) with parapneumonic effusions or pleural empyema, and 13 patients (14%) with exudative pleural effusions due to other causes (4 acute pleuritis, 3 postcardiac injury syndrome, 3 after local surgery, 1 collagen disease, 1 pleural tuberculosis, 1 chylothorax).

Of the patients diagnosed with pleural effusion due to heart failure, 18 (72%) suffered from systolic heart failure with a median left ventricular ejection fraction of 30% (25th and 75th percentiles: 25 to 40%), 4 patients (16%) had acute decompensated left ventricular valvular defects of grade II and III and 3 patients (12%) presented with lung congestion due to severe left ventricular diastolic dysfunction associated with pulmonary venous hypertension established by heart catheter examination.

As expected, patients with cardiac transudates were of higher age, more often had a history of chronic heart failure, myocardial infarction, renal failure or diabetes mellitus, more often presented with bilateral effusions and had significantly lower pleural fluid levels and pleural fluid to serum ratios of protein, lactate dehydrogenase and cholesterol (see Table 2). However, patients with exudative effusions suffered frequently from comorbid illnesses with 27 (40%) of them having a history of chronic, non-decompensated heart failure.

Levels of NT-proBNP measured in pleural fluid and in serum correlated closely (Spearman coefficient of rank correlation 0.96, p<0.001; see Figure 1).

Median levels of NT-proBNP in pleural fluid or serum among patients with pleural effusion due to heart failure were significantly higher (in pleural fluid: 10427 ng/l, 7366 to 21844 ng/l; in serum: 10791 ng/l, 6588 to 20263 ng/l) than in patients with non-cardiac causes (in pleural
Measurement of NT-proBNP in pleural fluid and in serum displayed high diagnostic accuracies as shown by ROC curve analysis (area under the curve [AUC] = 0.98 for both; see Figure 3). Linear discriminant analysis after logarithmic transformation of NT-proBNP levels revealed nearly identical cross-validated discriminative properties for measurement in pleural fluid and serum. As determined by ROC curve analysis, a NT-proBNP cut-off value of 4000 ng/l in pleural fluid and serum had a sensitivity of 92% (95% confidence interval [CI]: 74% to 99%) and 88% (95% CI: 69% to 97%) and a specificity of 93% (95% CI: 84% to 98%) each with an overall diagnostic accuracy of 92% (95% CI: 85% to 97%) and 91% (95% CI: 84% to 96%), respectively (see Table 3).

In our patient group, where transudative effusions were caused by heart failure only, we were able to calculate the comparative diagnostic properties of the criteria of Light to detect cardiac effusions in a post-hoc analysis: The finding of a transudate was associated with a low sensitivity of 64% (95% CI: 43% to 82%). As expected, their specificity to exclude exudative effusions was high at 93% (95% CI: 84% to 98%), leading to an overall diagnostic accuracy of 85% (95% CI: 76% to 92%). 9 of the 25 patients (36%) with pleural effusion due to heart failure were falsely classified as exudates by the criteria of Light. All of them had NT-proBNP values of > 4000 ng/l. The characteristics of these 9 patients are shown in Table 4, all except one received diuretic therapy. On the other hand, all 5 patients with exudates falsely labelled as transudates by the criteria of Light had NT-proBNP values of < 4000 ng/l, 3 of them having confirmed malignant effusions.

Discussion:
The serum level of NT-proBNP is an established marker for the assessment of cardiac function and has successfully been used as tool for diagnosis and management of acute and chronic heart failure including systolic and diastolic left ventricular dysfunction and valvular disease (6, 7, 8, 9, 14). Especially in the emergency care setting, NT-proBNP levels are a valuable addition to clinical judgement for the identification or exclusion of acute heart failure as cause of dyspnoea (6). Measurement of BNP and NT-proBNP in serum was shown to perform equal properties in predicting acute heart failure (15).

In patients presenting with pleural effusion, our findings demonstrate that levels of NT-proBNP in serum and pleural fluid are significantly elevated by about 10-fold in patients, in whom acute decompensated left heart failure could be identified as cause of the effusion, when compared to patients with non-cardiac effusions. Moreover, elevated NT-proBNP levels displayed a high sensitivity and specificity in detecting cardiac transudates in this patient group over a relatively large range of cut-off values (see Figure 3).

When compared to the finding of a transudate by the established criteria of Light in our patients group, where transudative pleural effusions were only attributed to heart failure, we found NT-proBNP levels in serum and in pleural fluid to discriminate more accurately between cardiac versus non-cardiac effusions. In accordance with the literature, the criteria of Light exhibited a high ability for excluding exudates, but the finding of a transudate showed a low sensitivity of 64% to identify cardiac effusions. In patients misclassified by the criteria of Light in either way, NT-proBNP values always were able to correctly detect or exclude cardiac origin of the effusion (see Results). Thus, the criteria of Light remain the diagnostic standard to exclude exudative effusions, but measurement of NT-proBNP proved to be a valuable supplementary diagnostic tool, which according to our data strongly suggests a cardiac origin of the effusion at values > 4000 ng/l, and on the other hand makes cardiac effusions very unlikely at values < 4000 ng/l (see Figure 3).

These data are in principal accordance with the other studies examining this issue.
One recently published study by Gegenhuber et al. (12) examined plasma levels of BNP in 64 prospectively enrolled consecutive patients, 31 with pleural effusions due to heart failure, 2 with transudative effusions of different origin and 24 with exudative effusions. They reported a diagnostic accuracy for plasma BNP levels of 93% to identify cardiac effusions, comparable to the data we found with NT-proBNP.

Tomcsányi et al (10) prospectively compared NT-proBNP levels in pleural fluid and serum in 14 patients with pleural effusion due to congestive heart failure and 14 patients with pleural exudates of various causes. In this small study, the authors found significantly higher levels of NT-proBNP in either serum or pleural fluid in patients with cardiac effusions (median values of 6295 versus 277 ng/l in pleural fluid and 5713 versus 236 ng/l in serum) and suggested a diagnostic cut-off point for detecting cardiac transudates of between 599 and 1457 ng/l. However, patients with exudative effusions and coexisting chronic heart failure were excluded from their analysis.

Porcel et al (11) retrospectively examined NT-proBNP levels in pleural fluid of a cohort of 117 patients after thoracentesis, randomly selected from a larger database, of whom 44 (38%) were diagnosed to have pleural effusion due to acute heart failure. Consistent with our data, the authors detected significantly higher median levels of NT-proBNP in cardiac effusions (6931 ng/l) when compared to exudative effusions (292 ng/l). From their data they calculated a diagnostic cut-off point of 1500 ng/l for detecting cardiac transudates with a sensitivity of 91% and a specificity of 93%. NT-proBNP levels in serum were not measured in their study.

As in our study, both authors measured NT-proBNP levels by a commercial electrochemiluminescence immunoassay on an Elecsys 2010 (Roche) analyser.

Whereas NT-proBNP levels of our patients with pleural effusions due to heart failure are comparable to those by the former two groups, we detected about three times higher median NT-proBNP values in our patients with exudative effusions (see Table 2), resulting in a suggested cut-off value which subsequently is about threefold higher. Unlike the other two
studies our prospective data present the results from non-selected consecutive patients with pleural effusion. This led to the inclusion of a considerable proportion of 40% of the patients with non-cardiac exudative effusions suffering from coexisting mild to moderate chronic, but not decompensated heart failure including chronic right and / or left ventricular dysfunction, chronic cardiac valve disease and / or chronic atrial fibrillation (see Table 2), conditions known to be associated with elevated NT-proBNP levels. Moreover, of our patients with exudative effusions 19% had a history of diabetes mellitus and 16% of impaired renal function, diseases that also can cause elevated NT-proBNP-levels (16). The discrepancy in NT-proBNP levels might be explained by the high frequency of these comorbid conditions in our non-selected patient group, frequently suffering from thoracic malignancies and pleural empyema, which mainly occur in elderly patients with multiple comorbidities. Thus they possibly represent a more “real” group of control subjects. This suggestion is supported by the finding of a study evaluating NT-proBNP concentrations in serum as diagnostic tool to detect a reduced left ventricular systolic function in a cohort of 2193 consecutive hospital inpatients (17). The authors divided patients into three groups and found median NT-proBNP values of 7273 ng/l in patients with LVEF ≤ 40%, 2368 ng/l in patients with LVEF > 40% and ≤ 50% and 685 ng/ml in patients with LVEF > 50%. Based on this data of consecutive hospitalised patients, the median serum NT-proBNP level of 989 ng/l seen in our patient group with non-cardiac pleural effusions and a high frequency of comorbidities including non-decompensated chronic heart failure lies well within the expected range. Thus, our suggested higher cut-off value of 4000 ng/l might be more appropriate to accurately predict cardiac origin of pleural effusions with minimizing the risk of overseeing additional underlying diseases. On the other hand we cannot exclude that our results and the corresponding cut-off values have been biased as well due to the limitations of our study discussed below. Thus, further prospective trials on large, non-selected patient groups are needed to confirm these issues.
The other interesting finding of our study is the close correlation of NT-proBNP levels in pleural fluid and serum, leading to equal diagnostic properties in identifying cardiac effusions. This confirms the result of the data of Tomcsányi et al (10), who found a comparably high correlation. To date the origin of NT-proBNP in pleural fluid is unclear, although 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 (18). Thus there seems to be no additional value of measuring NT-proBNP in pleural fluid.

There are several limitations to our study. First, examining a relatively small prospective group of 93 consecutive patients, our results need to be confirmed by larger studies. Second, because the study was designed as pilot study to prospectively examine the diagnostic discriminative properties of NT-proBNP between cardiac versus non-cardiac pleural effusions and to suggest cut-off values for further studies, the small subset of 8 patients in whom a definite diagnosis could not be established from the hospital records had to be excluded from the analysis, although this might be a subgroup of potential interest in studying the predictive properties of NT-proBNP levels. Third, we were not able to include any transudative pleural effusions of non-cardiac origin like effusions associated with hepatic or renal disease. Examining the diagnostic utility of NT-proBNP in this patient group would be of particular interest, as the criteria of Light are not able to discriminate between them. Moreover, the preliminary data from Porcel et al (11) suggest a potential value of NT-proBNP for this indication. Fourth, as the diagnosis of pleural effusion due to heart failure is usually based on clinical criteria supported by the finding of a transudate, we cannot conclude from our data, whether NT-proBNP measurement would be of any additional diagnostic value when compared to the clinical impression of the treating physician; this issue remains subject to further studies (18).
Fifth, there are several factors related to the study design potentially biasing our results: Echocardiography was performed in all patients with suspected pleural effusion due to heart failure; in all other patients this was left to the attending physician. Thus, in a minority of 25 of the 68 patients diagnosed to have non-cardiac effusions, who all were without any clinical signs suggestive of heart failure, echocardiography had not been performed and underlying heart disease, although less probable, cannot be entirely excluded. As we included a small proportion of patients with pleural effusion due to heart failure or malignancy being referred for therapeutic rather than diagnostic thoracentesis, this might have biased the disease prevalence of heart failure in our patient group and thus the diagnostic properties calculated for NT-proBNP. Finally, although the study-relevant diagnosis was established independently from the biochemical data, the attending physicians treating the patients were not blinded to the NT-proBNP results. It cannot be excluded, that this diagnostic information might have influenced further diagnostic approaches and thus again potentially biased the study results.

In conclusion, NT-proBNP levels either in pleural fluid or in serum showed a high diagnostic accuracy in identifying cardiac transudates. Thus, they might be valuable additional diagnostic tools to detect or exclude cardiac origin of pleural effusions. From our data it can be suggested, that cut-off levels in non-selected patient groups might be higher than those previously reported (10, 11) for not overseeing underlying causes other than heart failure in the often multimorbid patients presenting with pleural effusions. However, larger prospective studies are needed to confirm the cut-off points in non-selected patient groups and to examine the discriminative properties of NT-proBNP in differentiating transudates of non-cardiac origin. Also it would be interesting to compare the diagnostic properties of NT-proBNP with the clinical suspicion of the treating physician in addition to the finding of the criteria of Light in identifying cardiac effusions.
As NT-proBNP levels in serum and pleural fluid closely correlate and measurement of NT-proBNP in serum showed equally good diagnostic properties, examination in serum only might be a promising diagnostic tool to suggest pleural effusion due to heart failure with an acceptable positive predictive value, leading to the possibility to potentially postpone diagnostic thoracentesis in this situation until a trial of diuretic therapy has been performed. However, this strategy should be addressed in further prospective trials.
Reference list


Figure legends:

Figure 1: Correlation of serum and pleural effusion levels of NT-proBNP (logarithmic scale). Spearman coefficient of rank correlation 0.963 (95% CI: 0.944 to 0.975), p<0.001. Regression equation according to Passing and Bablok method (13): NT-proBNP in serum = -12.967 + 0.959 × NT-proBNP in pleural fluid; Intercept A = –12.967 (95% CI: –59.000 to 12.414), Slope B = 0.959 (95% CI: 0.908 to 1.000).

![Figure 1: Correlation of serum and pleural effusion levels of NT-proBNP (logarithmic scale).](image)

Figure 2: Box plots showing the medians and quartiles of NT-proBNP levels in serum and pleural effusion according to clinical diagnosis. Outliers (open circles) and extremes (stars) are plotted separately.

![Figure 2: Box plots showing the medians and quartiles of NT-proBNP levels in serum and pleural effusion according to clinical diagnosis. Outliers (open circles) and extremes (stars) are plotted separately.](image)
Figure 3: ROC curve of NT-proBNP levels in serum and pleural effusion for differentiating between cardiac and non-cardiac pleural effusions. AUC = 0.98 for both, NT-proBNP in serum and in pleural effusion (95% CI: 0.96 to 1.00).
Table 1: The criteria of Light for defining transudative pleural effusions (1)

Pleural fluid is considered a transudate, if all three of the following criteria are met:
- Pleural fluid to serum protein ratio ≤ 0.5
- Pleural fluid to serum lactate dehydrogenase (LDH) ratio ≤ 0.6
- Pleural fluid LDH level ≤ 2/3 of the upper limit of normal for serum LDH level
Table 2: Characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cardiac effusions (n=25)</th>
<th>Non-cardiac effusions (n=68)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (25th to 75th Percentile) or Number (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical data:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>72 (64-83)</td>
<td>65 (56-76)</td>
<td>0.027</td>
</tr>
<tr>
<td>Male sex</td>
<td>18 (72)</td>
<td>36 (53)</td>
<td>0.15</td>
</tr>
<tr>
<td>Bilateral effusions</td>
<td>15 (60)</td>
<td>22 (32)</td>
<td>0.019</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>10 (40)</td>
<td>2 (3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>History of chronic heart failure</td>
<td>24 (96)</td>
<td>27 (40)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>History of renal failure</td>
<td>11 (44)</td>
<td>11 (16)</td>
<td>0.011</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>12 (48)</td>
<td>13 (19)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Biochemical data:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural fluid protein (g/l)</td>
<td>20.4 (16.7-24.7)</td>
<td>35.6 (27.2-41.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pleural fluid/serum protein ratio</td>
<td>0.32 (0.27-0.46)</td>
<td>0.56 (0.45-0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pleural fluid lactate dehydrogenase (U/l)</td>
<td>98 (77-164)</td>
<td>326 (150-727)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pleural fluid/serum lactate dehydrogenase ratio</td>
<td>0.35 (0.28-0.52)</td>
<td>1.07 (0.54-2.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pleural fluid cholesterol (mmol/l)</td>
<td>0.70 (0.49-0.90)</td>
<td>1.63 (1.01-2.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pleural fluid/serum cholesterol ratio</td>
<td>0.15 (0.11-0.31)</td>
<td>0.42 (0.28-0.62)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pleural fluid NT-proBNP (ng/l)</td>
<td>10427 (7366-21844)</td>
<td>947 (372-1937)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum NT-proBNP (ng/l)</td>
<td>10791 (6588-20263)</td>
<td>989 (296-1691)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Criteria of Light:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transudative effusion</td>
<td>16 (64)</td>
<td>5 (7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1 criteria for exudate</td>
<td>5 (20)</td>
<td>15 (22)</td>
<td>1.0</td>
</tr>
<tr>
<td>2 criteria for exudate</td>
<td>2 (8)</td>
<td>16 (24)</td>
<td>0.139</td>
</tr>
<tr>
<td>3 criteria for exudate</td>
<td>2 (8)</td>
<td>32 (47)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Table 3: Predictive potential of NT-proBNP to classify transudative cardiac pleural effusions

Data are presented as number (%) with 95% confidence intervals

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predicted value</th>
<th>Negative predicted value</th>
<th>Overall accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP in pleural fluid &gt; 4000 ng/l</td>
<td>92% (74% - 99%)</td>
<td>93% (84% - 98%)</td>
<td>82% (63% - 94%)</td>
<td>97% (89% - 100%)</td>
<td>92% (85% - 97%)</td>
</tr>
<tr>
<td>NT-proBNP in serum &gt; 4000 ng/l</td>
<td>88% (69% - 97%)</td>
<td>93% (84% - 98%)</td>
<td>81% (62% - 94%)</td>
<td>95% (87% - 99%)</td>
<td>91% (84% - 96%)</td>
</tr>
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</table>
Table 4: Characteristics of patients with pleural effusion due to heart failure misclassified as exudates by the criteria of Light (Bold values = criteria for exudate according to Light)

<table>
<thead>
<tr>
<th>Age, sex</th>
<th>Diagnosis</th>
<th>Relevant comorbidities</th>
<th>Diuretics</th>
<th>P* protein (g/l)</th>
<th>P/S* protein</th>
<th>P* LDH (U/l)</th>
<th>P/S* LDH</th>
<th>P*NT-pro BNP (ng/l)</th>
<th>S*NT-pro BNP (ng/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>41, m</td>
<td>Cardiac shock after AMI*, LVEF* 25%</td>
<td>Acute RF*, embolic cerebral infarction</td>
<td>N</td>
<td>30.4</td>
<td>0.64</td>
<td>1332</td>
<td>2.06</td>
<td>34479</td>
<td>34302</td>
</tr>
<tr>
<td>83, w</td>
<td>Decompensated aortic valve stenosis III° and CHF* with LVEF* 40%, atrial fibrillation</td>
<td>None</td>
<td>Y</td>
<td>36.9</td>
<td>0.53</td>
<td>82</td>
<td>0.30</td>
<td>9785</td>
<td>8998</td>
</tr>
<tr>
<td>73, m</td>
<td>Decompensated CHF* (LVEF* 40%) under intensive care (cerebral bleeding) after AMI*</td>
<td>Acute cerebral bleeding, Diabetes mellitus</td>
<td>Y</td>
<td>32.6</td>
<td>0.55</td>
<td>70</td>
<td>0.34</td>
<td>9269</td>
<td>12102</td>
</tr>
<tr>
<td>39, m</td>
<td>Recurrent pleural effusions from CHF* with LVEF* 35% 8 years after heart transplantation</td>
<td>Chronic compensated RF*</td>
<td>Y</td>
<td>26.8</td>
<td>0.44</td>
<td>98</td>
<td>0.63</td>
<td>8305</td>
<td>7358</td>
</tr>
<tr>
<td>92, w</td>
<td>Cardiac shock after AMI*</td>
<td>Diabetes mellitus</td>
<td>Y</td>
<td>12.2</td>
<td>0.27</td>
<td>224</td>
<td>0.44</td>
<td>51537</td>
<td>44247</td>
</tr>
<tr>
<td>64, m</td>
<td>Decompensated aortic valve insufficiency III° from endocarditis</td>
<td>COPD, Diabetes mellitus, chronic compensated RF*</td>
<td>Y</td>
<td>38.4</td>
<td>0.60</td>
<td>456</td>
<td>0.85</td>
<td>10892</td>
<td>6799</td>
</tr>
<tr>
<td>70, m</td>
<td>Decompensated CHF* with LVEF*</td>
<td>rectal carcinoma, bone metastases</td>
<td>Y</td>
<td>15.0</td>
<td>0.24</td>
<td>206</td>
<td>0.13</td>
<td>40356</td>
<td>42132</td>
</tr>
<tr>
<td>m</td>
<td>30% and aortic valve stenosis II°</td>
<td>(effusion without malignancy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>72, w</td>
<td>Decompensated CHF* with LVEF* 30%</td>
<td>Sepsis from infected angiopathic foot syndrome, Diabetes mellitus</td>
<td>Y</td>
<td>17.6</td>
<td>0.49</td>
<td><strong>596</strong></td>
<td><strong>2.64</strong></td>
<td>16812</td>
<td>29329</td>
</tr>
<tr>
<td>66, m</td>
<td>Decompensated CHF* with LVEF* 15%</td>
<td>Diabetes mellitus, chronic compensated RF*</td>
<td>Y</td>
<td>22.5</td>
<td>0.36</td>
<td><strong>180</strong></td>
<td><strong>0.64</strong></td>
<td>5429</td>
<td>6368</td>
</tr>
</tbody>
</table>

*P = pleural, S = serum, AMI = acute myocardial infarction, LVEF = left ventricular ejection fraction, RF = renal failure, CHF = chronic heart failure