Original Article
Eurasian Journal of Critical Care

The New Biomarkers Used in the Differentiation Between Transudate and Exudate Pleural Effusions

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Abstract

Etiological diagnosis of pleural effusion is sometimes easy and sometimes very difficult challenge. In most of patients with pleural effusion, the symptoms, signs and laboratory data are not pathognomonic for etiologic diagnosis. In a patient with an undiagnosed pleural effusion, the first question to answer is whether the fluid is a transudate or an exudate. This is usually determined by means of Light's criteria. In patients under diuretic treatment, Light's criteria misclassify transudates as exudates, but the pleural fluid NT-pro-BNP levels usually is above 1500 pg/mL in pleural effusions associated with heart failure.

Keywords: pleural effusion, new biomarkers, NT-pro-BNP

INTRODUCTION

Presented by Light et al.[1] to be used in the differentiation of exudates from transudates and also known as the Light's criteria, the criteria are still widely accepted and commonly used today although more than 40 years have passed since its definition. Light's Criteria: Exudative Effusions will have at least one or more of the following: Pleural fluid protein / Serum protein >0.5. Pleural fluid LDH / Serum LDH >0.6. Pleural fluid LDH > 2/3 Serum LDH Upper Limit of Normal. Despite the fact that the Light's criteria have been accepted as the first step towards the diagnosis of pleural effusions (PEs), concerns over the benefit of this approach have always been present since the creation of the criteria[2-5]. A few of the focus points of these concerns can be explained as follows:

1- Light et al.[1] reported the sensitivity of the criteria they defined in their original study as 99% and the specificity as 98% in determining exudates. In later studies, Light's criteria high sensitivity rates were supported but the specificity rates were emphasized to be lower than specified (65%-86%)[2,3]. Despite the superior differentiating power of the Light's criteria, it is known that approximately 20-30% of transudative PEs related to cardiac failure and cirrhosis were wrongly classified as exudates with the Light's criteria[6]. Majority of the cases falsely diagnosed as exudates were demonstrated to be patients receiving diuretic therapy, and diuretic therapy was shown to change the serum and PE biochemical parameters[7]. Is using biochemical parameters to differentiate between transudative and exudative PEs adequate and significant? What should be the primary approach if the clinical prediction contradicts with the biochemical diagnosis methods[8]?
2- Some etiological factors can cause both transudative and exudative PEs. In fact, the same patient sometimes may have two different concurring disorders. It is emphasized that in such cases, primarily clinical decisions should prevail biochemical approaches in differentiating between transudate and exudate[9].
3- Although rarely, transudative PE development or bloody transudative PE formation related to different pathologies is also possible in patients with malignancies. Because of the high LDH levels present in erythrocytes (containing LDH-1 isoenzyme), it is expected to raise the LDH levels in bloody transudative PEs and thus, the liquid can be wrongly classified as exudates (meeting exudate criteria)[10]. However, in a study where 23 patients with bloody PEs having an erythrocyte number of more than 100.000/mm^3 were enrolled, only a slight increase was demonstrated in the PE LDH-1 levels contrary to the expectations[11].
4- A threshold border level to be chosen for a test affects the test's sensitivity and specificity. Knowingly attempting to increase the sensitivity of a test will decrease its specificity and will start to give false positivity in more people. The sensitivity and specificity, and thus the false

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Received: 16.09.2019 • **Accepted:** 30.10.2019

positive and false negative numbers of any test are dependent upon the cutoff value chosen to determine exudative PEs. If the cutoff value is chosen high, all transudates will be determined as true but if it is chosen low, then all exudates will be determined as true. Using this approach, Heffner et al.[12] analysed the data of a total of 1448 patients in eight studies and concluded that the best cutoff values were, respectively, 0.5 for protein rate, 45% of the serum upper limit of normal for PE LDH level and 0.45 for LDH rate. At the same time in this meta-analysis, the authors showed that only two or three combinations of pleural fluid parameters (e.g. combination of LDH and cholesterol or combination of LDH, cholesterol and protein) had diagnosis rates similar to the Light criteria without a need for blood samples and with a lower cost.

5- Tests used in the differentiation or diagnosis of PEs should be cost-effective. For this reason, many studies focused on making the Light criteria more cost-effective without decreasing the accuracy of the diagnosis. In the first studies on the subject, the measurement of PE cholesterol level alone was claimed to be used as an alternative to the Light criteria in the differentiation of transudates and exudates as a cost-effective test[13]. However, these dates could not be verified in the later studies[2,14]. Furthermore, studies on the measurement of PE cholesterol level are still ongoing today but none of the results obtained from the studies show consistency with one another. Hamel et al.[15] reported in their recent study that when the cutoff value for the PE cholesterol level was taken as >45 mg/dL, the sensitivity was 97.7% and the specificity was 100% in the differentiation of transudate-exudate. In a systematic compilation published a very short time ago, the most specific findings for exudate diagnosis were determined to be PE cholesterol level being >55 mg/dL, PE/serum cholesterol rate being >0.3 and PE LDH level being >200 U/L[16].

6- There is a need for new biomarkers that could be used in the differentiating diagnosis (e.g. malignant, tuberculosis, parapneumonic pleurisy) within the exudative PEs after the transudate-exudate differentiation; that could lead the way for diagnostic (e.g. pleura biopsy, thoracoscopy) or therapeutic (e.g. recurring thoracentesis, chest tube insertion) procedures; that could reveal the etiological cause in malignant PEs (malignant mesothelioma, lung cancer metastasis or metastasis from extrapulmonary malignancies); that could demonstrate early whether the non-purulent parapneumonic PEs are complicated or not.

In light of these controversial subjects, we will talk about new biomarkers proposed for the diagnosis of exudative PEs and presented as a contribution or an alternative to the Light criteria in the following parts of the article. Although there are dozens of new biomarkers used in studies related to PEs, unfortunately very few of them conform to the criteria of ideal biomarkers that could be used clinically, and primarily these will be discussed in this paper. An ideal biomarker is one that can easily be measured, that has a reasonable price that helps in decisions, that is repeatable and that gives the same results each time it is repeated[17].

New Biomarkers

While the Light criteria are widely used in clinical practice, it can particularly wrongly classify more than 25% of transudative bloody PEs, developing in patients receiving diuretic therapy due to cardiac failure[18]. After albumin and protein gradient calculations were started to use, the wrong classification of transudative PEs in patients receiving diuretic therapy was decreased. If albumin gradient (serum-PE albumin difference) is >1.2 g/dL or protein gradient (serum-PE protein difference) is >3.1 g/dL, PE is classified as transude. However, these gradient calculations should not be used as a starting parameter due to their low sensitivity. In PEs classified wrongly as exudates with the Light criteria despite the clinical situation supporting transude, calculation of albumin or protein gradients in PEs is recommended[2,19,20]. Bielsa et al.[6] reported that albumin gradients classified correctly more PEs compared to protein gradient (83% vs. 55% of wrong classifications). Nevertheless, in clinical practice it is recommended that first protein gradient is calculated and that if no result is obtained, albumin gradient is calculated or N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) level is measured because protein level is measured at baseline due to the purposes of the Light criteria[10].

Natriuretic Peptides

Natriuretic peptides (ANP, proANP, BNP, NT-pro-BNP) are neurohormones used to help the diagnosis of cardiac failure and excreted by myocardium myocytes depending on the increased pressure or volume burden[21]. In clinical practice, while serum BNP level being lower than 100 pg/mL or NT-pro-BNP level being lower than 300 pg/mL excludes the diagnosis of cardiac failure, BNP level being higher than 500 pg/mL or NT-pro-BNP level being higher than 450-1800 pg/mL (depending on conditions such as threshold value age, gender, renal failure and increasing with age) supports cardiac failure diagnosis[22].

Increased ***NT-pro-BNP*** levels in PEs due to cardiac failure were first demonstrated in 2004 by Porcel et al.[23]. Many later studies also support the use of PE NT-pro-BNP level in determining PEs developing due to cardiac failure[24-26]. In three different studies, Porcel et al.[21] measured NT-pro-BNP levels in 150 PEs developing due to cardiac failure and in 158 PEs related to factors other than cardiac failure (58 ma-

lignant, 31 parapneumonic, 28 tuberculosis, 18 hepatic, 13 pulmonary embolism, 5 transudates with other reasons and 5 exudates with other causes). They reported that median NT-pro-BNP levels were significantly higher in PEs related to cardiac failure (6203 pg/mL) than PEs related to other causes (342 pg/mL). The best cutoff value for the diagnosis of PEs related to cardiac failure was determined to be 1300 pg/mL with ROC analysis and for this cutoff value, sensitivity was calculated as 93.3%, specificity as 89.9%, and the area under ROC curve as 0.96. If the cutoff value is taken as 1500 pg/mL, the sensitivity (91%) and the specificity (93%) of the test becomes more diagnostic for cardiac failure. Liao et al.[27] compared the NT-pro-BNP levels in ten patients, each with PEs related to cardiac failure, pulmonary thromboembolism, coronary artery bypass surgery and malignancy, and they reported that PE NT-pro-BNP levels were above 1500 pg/mL in all PEs related to cardiac failure and that they were below this level in all PEs related to other causes. In the meta-analysis of data from a total of 1120 PEs (429 developing secondary to cardiac failure and 691 developing due to causes other than cardiac failure) obtained from 10 studies, including the studies by Seyhan et al.[28] and Bayram et al.[29] from Turkey, Janda and Swiston[30] calculated the sensitivity of NT-proBNP as 94% (95% CI: 90-97), the specificity as 94% (95% CI: 89-97) and area under ROC curve as 0.98 (95% CI: 0.96-0.99). The authors stated in the conclusion of this meta-analysis that the best diagnosis threshold value for PE NT-pro-BNP was ≥1500 pg/mL. This threshold is widely accepted and commonly used today.

In a study by Cincin et al.[26], 8 of 21 PEs related to cardiac failure (38.1%) was wrongly classified as exudate. 5 of those were patients receiving diuretic therapy prior to thoracentesis. It was reported that PE NT-pro-BNP levels were significantly much higher in the ones wrongly classified as exudates (2024 pg/mL) than actual exudates (367 pg/mL). Porcel et al.[31] reported that 31 of 129 PEs related to cardiac failure (24%) were wrongly classified as exudates with the Light criteria, that NT-pro-BNP levels provided diagnosis accuracy in 27 of these 31 PEs (87%), that the diagnosis accuracy of protein gradient was 53% and of albumin gradient was 79%. That NT-pro-BNP levels were measured to be significantly much lower (551 pg/mL) in other conditions (6931 pg/mL) such as cirrhosis causing transudative PEs in another study by the same researchers brings forward NT-pro-BNP as a biomarker specific to PEs related to cardiac failure[23]. That there is a strong correlation between serum and PE NT-pro-BNP levels reiterates NT-pro-BNP being a good biomarker for cardiac PEs more. Bayram et al.[29] measured NT-pro-BNP levels in 133 patients and calculated the correlation covariance between serum and PE as 0.91. Similarly, four other studies on the subject support the strong correlation between serum and PE for NT-pro-BNP test, and the correlation covariance values in these studies vary between 0.90 and 0.95[26,31-33].

Another reason making NT-pro-BNP a more ideal biomarker for cardiac PEs is their superiority to BNP. Several studies investigated the diagnostical value of PE BNP in the differential diagnosis of PEs and compared it to NT-pro-BNP head-to-head. In the first study on the subject, BNP and NT-pro-BNP levels of 90 PEs related to cardiac failure and 91 PEs related to other causes were measured. When the cutoff value for PE ***BNP*** level in determining PEs related to cardiac failure was taken as >115 pg/mL, the sensitivity was calculated to be 74% and the specificity to be 92%. These values were lower values compared to PE NT-pro-BNP. Furthermore, area under ROC curve was found to be lower in BNP (AUC: 0.90) than in NT-pro-BNP (AUC: 0.96), and the correlation between BNP and NT-pro-BNP was shown to be weak (r=0.78)[34]. In another study conducted later, the facts that BNP (AUC=0.70) was a weaker test than NT-pro-BNP (AUC=0.84) in determining PEs developing due to cardiac failure and that there was a weaker positive correlation (r=0.57) between these two tests were supported[35]. In a recent study, Marinho et al.[36] investigated 34 PEs related to cardiac failure and 43 PEs related to other causes and reported that BNP levels were significantly much more higher in PEs developing due to cardiac failure (386 pg/mL) than PEs related to other causes (43 pg/mL). In this study, when the cutoff value for PE BNP level in determining PEs related to cardiac failure was taken as >127 pg/mL, sensitivity was calculated to be 97%, specificity to be 88% and AUC to be 0.98. Another superior aspect of NT-pro-BNP to BNP is the in-vitro stabilization process. NT-pro-BNP can remain stable in in-vitro environments after serum or PE sample is taken (1-2 hours) compared to BNP (20 minutes), which provides NT-pro-BNP with a measurement advantage and superiority[34].

The diagnostical value of the other two members of natriuretic peptide family, ***midregional proatrial natriuretic peptide (MR-proANP)*** and midregional ***proadrenomedullin (MR-proADM)*** in PEs developing due to cardiac failure was recently investigated by Porcel et al.[37]. The researchers measured the levels of MR-proANP, MR-proADM and NT-pro-BNP in a total of 185 PEs, 95 of which were related to acute decompensated cardiac failure and reported that the diagnostical value of MR-proANP was closer to NT-pro-BNP but the diagnostical value of MR-proADM was very low. In the diagnosis of PEs related to cardiac failure, when the best cutoff value for MR-proADM was taken as >2.5 nmol/L, sensitivity was 60%, specificity was 56% and AUC was =0.620; when the best cutoff value for MR-proANP was taken as >260 pmol/L, sensitivity was 84%, specificity was 83% and AUC was =0.918; and when the best cutoff value for NT-pro-BNP was taken as >1700 pg/mL, sensitivity was 92%, specificity was 82% and AUC was =0.935.

In summary, NT-pro-BNP, a member of natriuretic peptide family, is an ideal biomarker that could be used in determining whether the PEs that are wrongly classified with the Light criteria but clinically considered to be related to

cardiac failure are related to cardiac causes or not because of the following reasons: that it can differentiate cardiac-related PEs from exudates and other transudate causes, that it is superior to protein gradient and albumin gradient in differentiating PEs wrongly classified as exudates, that there is a strong positive correlation between the serum and PE levels of the test, and that it has a measurement advantage because it can stay for a longer time in an in-vitro environment compared to BNP. The best diagnosis threshold value that is widely accepted and commonly used for PE NT-pro-BNP today is ≥1500 pg/mL. BNP and MR-proADM, the other members of the family, have no diagnostical superiority to NT-pro-BNP. That MR-proANP has a close diagnostical value to NT-pro-BNP brings to mind the hypothesis that this test could be superior to NT-pro-BNP in distinguishing cardiac-related liquids from liquids of other nature in the future, and there is a need for new studies that are well-planned and that can verify or exclude this possibility.

Ischemia Modified Albumin

Ischemia modified albumin (IMA) is a new biomarker that is shown to be better than classical markers such as troponin and creatinine kinase MB in revealing ischemia and that is studied to be used in the early diagnosis of ischemic heart diseases. There are only 2 studies on the measurement of IMA concentration in PEs, both of which were conducted in Turkey and published recently. Both of the studies reported that there was an increased IMA concentration in transudative PEs and that IMA was a good biomarker to be used in the differentiation of transudates and exudates. The first study was conducted by Ozsu et al.[38], and this study investigated the IMA levels in PEs, 10 of which were related to cardiac failure and 30 of which were related to causes other than cardiac failure (10 pulmonary thromboembolism, 10 parapneumonic, 10 malignant). The researchers reported that IMA concentration was significantly higher in PEs related to cardiac failure than PEs related to other causes and that the sensitivity of IMA was 90%, specificity was 80% and area under ROC curve was 0.927. This study reported that there was not a strong correlation between serum and PE IMA levels (r=0.540) but measurement of IMA levels could help in differentiating cardiac-related liquids. In the second study by Dikensoy et al.[39], more PE cases were included (total 160 PE; 50 transudate and 66 exudate) and it was reported that IMA concentration was significantly higher in transudates (7986 ng/mL) than exudates (3376 ng/mL) and that when the cutoff value was taken as >4711 ng/mL, the sensitivity was 82%, specificity was 78% and area under ROC curve was 0.837 in differentiating between transudates and exudates. The study found no difference between the IMA levels of transudates related to cardiac failure and transudates related to other causes. There was no significant correlation detected between serum and PE IMA levels. While the results of both studies had no superiority to the Light criteria, the results indicate that IMA can be a candidate as a good biomarker.

Soluble Urokinase Plasminogen Activator Receptor

Another biomarker that was investigated to be used in differentiating cardiac-related PEs from PEs related to other causes is soluble urokinase plasminogen activator receptor (suPAR). suPAR is actually a newly discovered inflammatory biomarker, and the only study published on its diagnostical value in cardiac PEs was conducted by Ozsu et al[40]. In the study that included 18 PEs developing due to cardiac failure and 56 PEs developing due to other causes, it was detected that suPAR was significantly lower in cardiac-related PEs (11.8 [5.4-28.9] ng/mL) than PEs of other causes (26.7 [8.2-102.8] ng/mL) and that when the cutoff value for suPAR level was taken as ≥17.6 ng/mL to exclude the causes other than cardiac failure, sensitivity was 88%, specificity was 83% and AUC was 0.878.

Others

Apart from these biomarkers, the following have been studied in the differentiation of transudates and exudates so far: alkaline phosphatase, bilirubin, creatinine kinase, uric acid, PE protein electrophoresis, acute phase proteins, pseudocholinesterase, PE/serum cholinesterase rate, cholinesterase, cytokines, HDL/LDL rate, triglyceride, cholesterol, glycosaminoglycan, copeptin, YKL-40 and ceruloplasmin. However, these markers were not shown to be superior to the Light criteria or when repeated, similar results were not obtained, or the diagnostical values could not be verified in later studies.

CONCLUSION

It is sometimes hard to reveal the cause of PE using routine methods. Despite the fact that the Light criteria have been accepted as the first step towards the diagnosis of pleural effusions (PEs), there are concerns over the benefit of this approach. There are new biomarkers proposed for the diagnosis of exudative PEs and presented as a contribution or an alternative to the Light criteria. An ideal biomarker is one that can easily be measured, that has a reasonable price that helps in decisions, that is repeatable and that gives the same results each time it is repeated[17]. Although there are dozens of new biomarkers used in studies related to PEs, only NT-pro-BNP, a natriuretic peptide conform to the criteria of ideal biomarkers that could be used clinically. NT-pro-BNP, a member of natriuretic pep-

tide family, level of pleural effusion being above 1500 pg/mL could be used in determining whether the PEs that are wrongly classified with the Light's criteria but clinically considered to be related to cardiac failure.

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