



## Original Article

# Diagnostic Value of N-Terminal Pro-Brain Natriuretic Peptide in Pleural Effusions of Cardiac Origin

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## ABSTRACT

**Introduction:** The diagnosis of cardiogenic pleural effusion (PE) is often difficult to make. The objective of our study was to evaluate the diagnostic usefulness of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in PE patients with heart failure, in pleural fluid (PF) and serum (S), and to compare the cholesterol in pleural fluid (CHOL PF) and in serum (CHOL S) with the Light criteria.

**Patients and methods:** All the biomarkers were evaluated in 398 PF (26.9% transudates). The area under the curve (AUC) quantified the overall diagnostic precision. The diagnostic precision of the different parameters was also assessed using the ROC curves.

**Results:** The AUC of the ROC for pleural fluid NT-proBNP was 0.894, with no significant differences with CHOL PF (0.914) or with the Light criteria (0.896). The sensitivity, specificity, the positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were 85.1% (94.1% for CHOL PF), 79.9% (90.2% for the Light criteria), 4.24 (7.27 for the Light criteria) and 0.19 (0.07 for CHOL PF), respectively. The combination of NT-proBNP in PF  $\geq$  276 pg/ml and CHOL PF  $\leq$  57 mg/dL managed to classify the highest number of PE correctly (sensitivity 97.8%, specificity 85.4%).

**Conclusions:** The diagnostic yield of NT-proBNP in cardiogenic PE is not superior to the CHOL PF or the Light criteria, although it could be diagnostic in transudates of another origin.

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## Valor diagnóstico de los niveles del N-terminal pro-péptido natriurético cerebral en los derrames pleurales de origen cardíaco

## RESUMEN

**Introducción:** El diagnóstico del derrame pleural (DP) cardiogénico plantea dificultades con frecuencia. El objetivo de nuestro estudio fue evaluar la utilidad diagnóstica en el DP en pacientes con insuficiencia cardíaca, de los niveles del fragmento N terminal del pro-péptido natriurético cerebral (NT-proBNP), tanto en líquido pleural (LP) como en sangre (S), y compararlo con los criterios de Light, el colesterol en líquido pleural (COL LP) y en suero (COL S).

**Pacientes y método:** Todos los biomarcadores fueron evaluados en 398 DP (26,9% trasudados). El área bajo la curva (ABC) cuantificó la precisión diagnóstica global; y mediante curvas ROC se evaluó la precisión diagnóstica de los diversos parámetros.

### Palabras clave:

Diagnóstico  
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NT-pro-BNP  
Derrame pleural

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**Resultados:** El ABC ROC para el NT-proBNP pleural fue 0,894, sin diferencias significativas con el COL LP (0,914) ni con los criterios de Light (0,896). La sensibilidad, especificidad, razón de probabilidad positiva (RPP) y razón de probabilidad negativa (RPN) fueron 85,1% (94,1% para COL LP), 79,9% (90,2% para los criterios de Light), 4,24 (7,27 para los criterios de Light) y 0,19 (0,07 para COL LP), respectivamente. La combinación del NT-proBNP en LP  $\geq$  276 pg/ml y COL LP  $\leq$  57 mg/dL consiguieron clasificar el mayor número de DP correctamente (sensibilidad 97,8%, especificidad 85,4%).

**Conclusiones:** El rendimiento diagnóstico del NT-proBNP en DP cardiogénicos no es superior al COL LP ni a los criterios de Light, aunque pudiera ser diagnóstico en trasudados de otro origen.

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## Introduction

More than 80% of patients with congestive heart failure (CHF) have pleural effusion.<sup>1</sup> This diagnosis is usually simple in a characteristic clinical context (typical clinical manifestations, bilateral pleural effusion and cardiomegaly), which make thoracentesis unnecessary.<sup>2</sup> However, pleural effusion of cardiac origin cannot be ruled out by the absence of cardiomegaly or the presence of unilateral effusion.<sup>3</sup> In the cases of atypical presentations, the finding of a transudate in the analysis of the pleural liquid helps establish the etiological diagnosis.<sup>4</sup>

Some researchers have demonstrated that a significant proportion of patients (20-25%) with pleural effusion due to CHF are mistakenly classified as exudates,<sup>5-7</sup> particularly if they have been previously treated with diuretics.<sup>8,9</sup> Thus, in these cases, the use of other alternative parameters has been proposed.<sup>10</sup>

In some series, pleural effusion secondary to CHF is the most frequent cause of pleural effusion,<sup>11</sup> and an interesting debate has recently been opened about the diagnosis of these pleuritis. Along this line, various studies have demonstrated the use of the determination of the N-terminal pro-brain natriuretic peptide (NT-proBNP), in the pleural fluid as well as in blood,<sup>11-18</sup> in the diagnosis of pleural effusion secondary to CHF. The levels of BNP are considered sensitive indicators of CHF exacerbations that cause acute dyspnea.<sup>19</sup>

The objective of this study is to evaluate the diagnostic utility of NT-proBNP, determined in the pleural fluid and blood, as well as the PF/S NT-proBNP ratio, in the pleural effusion of cardiac origin in comparison with that of the classic parameters used (Light criteria, pleural cholesterol and serum-pleural fluid albumin gradient).

## Patients and Methods

We prospectively studied all those patients admitted to the Pulmonology and Internal Medicine wards of our hospital due to pleural effusion between January 2006 and December 2009. Excluded were all those cases in which a definitive diagnosis was not reached and in those where it was considered that there could be more than one cause for pleural effusion. Although in order to establish the definitive diagnosis it was necessary to carry out several thoracentesis, only the results of the first were analyzed.

For all patients, in addition to recording their medical history and a physical examination, the necessary microbiological and anatomopathologic analyses were done in order to establish the definitive diagnosis. The patients included were classified based on the etiological diagnosis of the PE into the following groups: transudates of cardiac origin, other transudates – neoplastic, parapneumonic, tuberculous and miscellaneous using previously-established criteria,<sup>20</sup> regardless of the biochemical results obtained. In the case of neoplastic effusions, we also included the paramalignant effusions defined as those with histological diagnosis of neoplasm in other organs, with no cytohistological demonstration of neoplasm in the pleural space, in which other causes of pleural effusion were

ruled out, and coinciding with the onset of the neoplasia or with a demonstrated recurrence in other organs. The diagnosis of heart failure was established based on the data of the medical history, physical examination and complementary tests, including echocardiographic evidence of systolic dysfunction of the left ventricle (ejection fraction of the left ventricle  $\leq$  40%), severe valvular disease (grade II or III) or severe diastolic dysfunction of the left ventricle. The final clinical diagnosis was established after the evaluation of two of the authors (FJGB and JMAD), without knowing the results of the NT-proBNP. If there was no diagnostic agreement, it was considered that there may be more than one cause for the pleural effusion and the patient was excluded.

Due to the fact that it would not be practical, we did not take into account any of the factors that could influence in the biochemical results of the pleural fluid and blood (previous treatment with diuretics, concomitant diseases, etc.).

The pleural fluid and blood samples were obtained at the same time, on the first day of hospitalization with the patient fasting for more than 12 hours. Samples were collected in test tubes with no additives and frozen at  $-80$  C until they were processed. The pleural fluid samples were routinely sent for microbiology, cytology and biochemistry analyses. Pleural biopsies were performed with Cope or Abrams needles. The Light criteria for defining a pleural transudate were the following: pleural fluid/serum protein ratio (P PF/S)  $\leq$  0.5; lactate dehydrogenase ratio (LDH) PF/S  $\leq$  0.6 and LDH PF  $\leq$  2/3 of the normal upper limit of serum LDH (the three criteria should be met).<sup>4</sup> The ethics committee of our hospital approved the protocol, and informed consent was obtained from all the patients.

The levels of total protein, albumin, LDH and cholesterol (CHOL), in PF and S, were determined following the standard methodology in our hospital (ADVIA 2400, Siemens Healthcare Diagnostics Inc). The upper limit of normal for serum LDH was 320 IU/L. NT-proBNP was determined by means of electrochemiluminescence immunoanalysis (Modular Analytics E170, Roche Diagnostics) in accordance with the protocol of the manufacturer. This test has an interassay variation coefficient of 1.2-2.6% and a range of detection of 5-15,000 pg/mL.

## Statistical Analysis

The normality of the distributions was evaluated by means of the Kolmogorov-Smirnov test, with logarithmic transformation of the parameters with no Gaussian distribution. The comparison between the different groups of pleural effusion was done by the Bonferroni test. The diagnostic utility of the different parameters for distinguishing whether a pleural effusion was cardiogenic in origin was analyzed with the analysis of receiver operating characteristic (ROC) curves, comparing the area under the curve.<sup>21</sup> The diagnostic performance of the different parameters, depending on the cut-points obtained from the ROC curves (see results) was evaluated based on sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR). The correlation between the pleural and serum levels of NT-proBNP was analyzed with Spearman's test. The prediction capacity of the final diagnosis was determined by

**Table 1**  
Etiology of the pleural effusions (n=398)

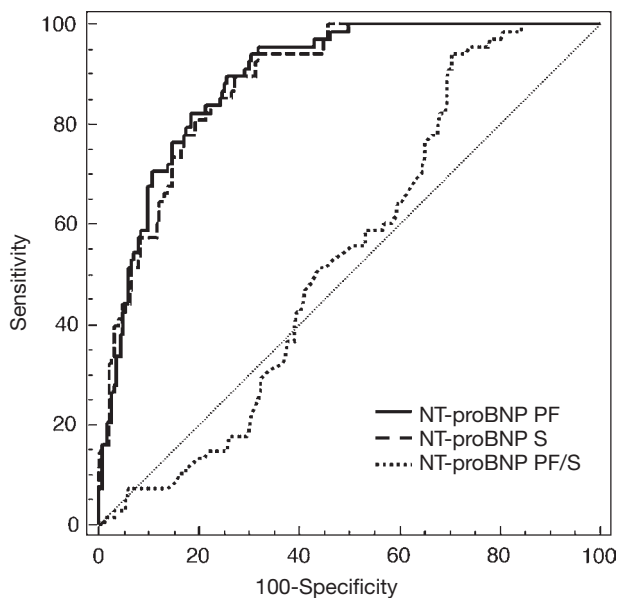
<b>Transudates</b>	
Congestive heart failure	107
Other transudates	94
Cirrhosis of the liver	13
Nephrotic syndrome	11
	2
<b>Exudates</b>	
Neoplastic	291
Parapneumonic	108
Tuberculous	57
Miscellaneous	50
	76

means of multiple logistic regression models, combining NT-proBNP with the remaining pleural fluid parameters. All the statistical analyses were completed with the EDCALC® program, Version 11.1.1.0. For the results of the ROC curves generated by the MEDCALC® program, the cut-point selected was that which gave the maximum precision (combining the least false positives and false negatives). A p value < 0.05 was considered significant.

## Results

During the study period, 470 patients were included. Seventy-two patients (15.3%) were excluded: in 50 patients (10.6%), no final diagnosis was reached and 22 (4.7%) presented two possible causes for pleural effusion. The etiology of the 398 pleural effusions that were ultimately admitted and their characteristics are presented in [Table 1] and [Table 2], respectively. Figure 1 shows the areas under the ROC curve of NT-proBNP PF, NT-proBNP S and the NT-proBNP PF/S ratio for diagnosing the cardiogenic pleural effusions. No differences were found between the first two, although there were differences found in PF/S NT-proBNP for the diagnosis of this type of pleuritis. NT-proBNP PF/S did not demonstrate any usefulness in the diagnosis of the transudates of cardiac origin.

Table 3 demonstrates the results obtained for the diagnosis of the pleural effusions of cardiac origin with each of the parameters studied. The best area under the ROC curve was obtained with CHOL PF. Although no significant differences were found either with the Light criteria or with NT-proBNP PF, there were differences with the



**Figure 1.** ROC curves of the parameters studied for the diagnosis of the cardiogenic effusions.

albumin gradient S-PF ( $p < 0.011$ ). The combination of parameters that provided a better diagnosis of the pleural effusions of cardiac origin were NT-proBNP PF  $\geq 276$  pg/mL and CHOL PF  $\leq 57$  mg/dL, with a sensitivity of 97.8%, a specificity of 85.4% and a diagnostic precision of 88.4% (date not shown).

Figure 2 details the levels of NT-proBNP PF (fig. 2A) and NT-proBNP S (fig. 2B) in the six groups studied. The levels of NT-proBNP PF correlate well with the serum levels, both in those of cardiac origin (Spearman's correlation coefficient 0.956;  $p < 0.0001$ ; fig. 3A) as well as in the other types of effusions considered as a group (Spearman's correlation coefficient 0.926;  $p < 0.0001$ ; fig. 3B).

The Light criteria erroneously classified 14.4% of the pleural effusions for the diagnosis of CHF, with no significant differences when compared with CHOL PF and NT-proBNP PF (table 4). CHOL PF better classifies the cardiogenic transudates, with significant differences compared with the Light criteria and the S-PF albumin gradient, but not with NT-proBNP PF ( $p < 0.0531$ ).

## Discussion

The objective of this study was to evaluate the effectiveness of NT-proBNP PF, NT-proBNP S and NT-proBNP PF/S in the diagnosis of pleural effusions of cardiac origin, compared with the Light criteria, CHOL PF and S-PF albumin gradient. Our results, in the largest series published to date, demonstrate that the determinations of these new parameters are not superior to the classic Light criteria or CHOL PF.

Both clinical evaluation as well as the use of the Light criteria help in the diagnosis of pleural effusions of cardiac origin but, even so, it has been seen that an important percentage of patients are misdiagnosed by these criteria.<sup>22</sup> In our study, the Light criteria erroneously classified 28.6% of the pleural effusions secondary to CHF, which coincides with what has been previously published.<sup>5-7</sup> Therefore, given the need for a more effective test for diagnosing effusions of cardiac origin, some publications have reported the usefulness of NT-proBNP PF (table 5), but in none has this diagnostic effectiveness been compared with that of CHOL PF.

As in previous studies, we have observed a good correlation between the levels of NT-proBNP in PF and S if we analyze only the effusions of cardiac origin (fig. 3A) as well as if we study them in their totality (fig. 3B). The areas under the ROC curve of the NT-proBNP PF and NT-proBNP S were less than those of CHOL PF and the Light criteria, although there were no significant differences in any of the cases (table 3). The diagnostic effectiveness that we have obtained with these parameters (NT-proBNP PF and NT-proBNP S) have been lower than that of the Light criteria (better specificity and PLR) and of CHOL PF (better sensitivity and NPR) due to the extensive overlapping of values compared with effusions of another etiology (fig. 2A and 2B). While the Light criteria better classify the exudates than the transudates (28.6% of errors in the diagnosis of pleural effusions secondary to CHF), and inversely CHOL PF (classifies erroneously 5% of the effusions of cardiac origin) (table 4), NT-proBNP PF is in an intermediate situation: it mistakenly classifies 14.9% of these pleuritis and 21.1% of the pleural effusions of non-cardiac origin. On the other hand, while the Light criteria and CHOL PF are not useful for distinguishing whether transudates are of cardiac origin or not (75% and 100% of errors), NT-proBNP PF is (8% errors).

Although it was not an objective of this present study, we have observed that the levels of NT-proBNP, in PF and in S are significantly higher in the group of other transudates than in the exudate group ( $p < 0.001$  and  $p < 0.05$ , respectively) (table 2). This difference could be justified because the first of these groups included 11 patients with cirrhosis of the liver, an entity that may present high values of this parameter.<sup>23,24</sup>

If we compare the results obtained with NT-proBNP PF in other studies, we observe that our effectiveness was lower<sup>11,12,14-18</sup> (table 5).

**Table 2**Characteristics of the participants in the study<sup>a</sup>

Characteristics	CHF (n = 94)	Other transudates (n = 13)	p <sup>b</sup>	Exudates (n = 291)	p <sup>b</sup>
Age, years	78 (35-93)	61 (42-81)	NS	65 (15-96)	<0.001
Men	60 (63.8%)	9 (69.2%)	NS	185 (63.6%)	NS
Proteins PF, g/L	2.3 (0.7-4.6)	1.5 (0.7-3.8)	NS	4.5 (1.2-6.7)	0.009
Proteins PF/S	0.38 (0.12-0.69)	0.25 (0.15-0.50)	NS	0.69 (0.22-1.04)	0.192
LDH PF, IU/L	111 (37-635)	93 (40-500)	NS	346 (54-29.000)	<0.001
LDH PF/S	0.44 (0.08-1.96)	0.37 (0.09-1.60)	NS	1.52 (0.09-143)	<0.001
Cholesterol PF, mg/dL	35 (6-87)	21 (9-142)	NS	86 (11-202)	<0.001
Cholesterol PF/S	0.22 (0.04-0.54)	0.16 (0.09-0.41)	NS	0.54 (0.07-1.39)	<0.001
Albumin gradient, g/L	1.8 (0.6-4.1)	1.9 (0.8-2.5)	NS	0.9 (0.01-4.4)	0.060
NT-proBNP S, pg/mL	3.442 (268-60.952)	510 (9.6-5.142)	<0.001	191 (10-14.631)	<0.001
NT-proBNP PF, pg/mL	3.918 (276-54.985)	417 (33-5.534)	<0.001	268 (6-60.213)	<0.001
NT-proBNP PF/S	1.11 (0.19-2.25)	1.09 (0.84-3.47)	<0.001	1.16 (0.02-22.5)	<0.001

CHF: congestive heart failure; LDH: lactate dehydrogenase; NS: not significant; NT-proBNP: N-terminal pro-brain natriuretic peptide; PF: pleural fluid; S: serum.

<sup>a</sup>The data are presented as mean (range) or number.<sup>b</sup>Significant differences (p < 0.05) between CHF and other transudates and between CHF and exudates.**Table 3**

Effectiveness of each of the parameters studied with their cut-points for the diagnosis of pleural effusion of cardiac origin

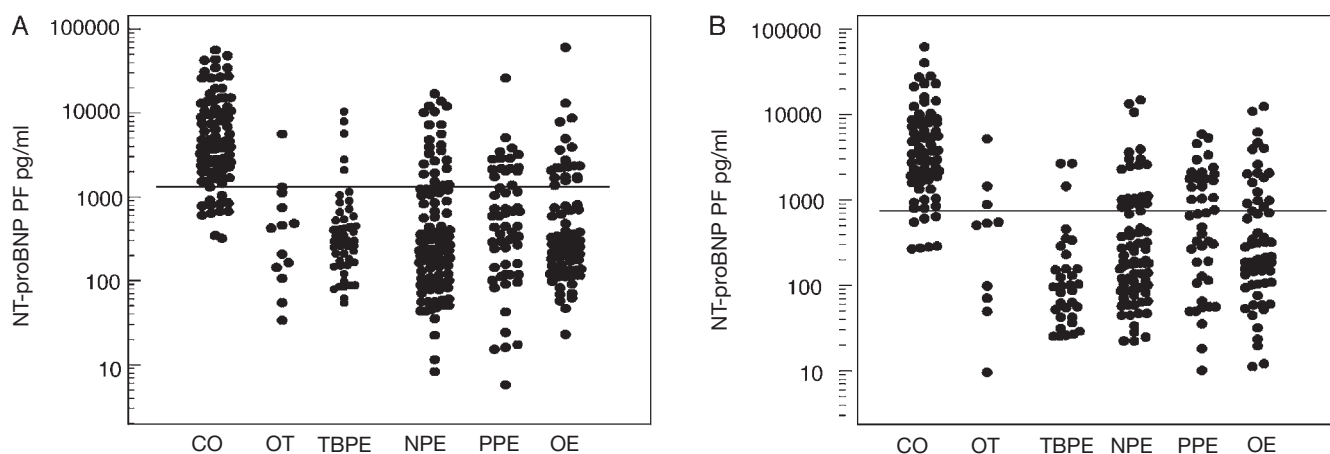
Biomarkers	Cut-point	Area under the ROC curve	Sensitivity %	Specificity %	Diagnostic precision %	PLR	NLR
NT-proBNP S (pg/mL)	>748	0.885 (0.843-0.919)	89.7 (79.9-95.8)	72.7 (66.3-78.4)	76.3 (69.2-79.3)	3.28 (2.9-3.7)	0.14 (0.07-0.3)
NT-proBNP PF (pg/mL)	> 1.409	0.894 (0.860-0.923) <sup>a</sup>	85.1 (76.3-91.6)	79.9 (75-84.3)	81.4 (78.2-83.4)	4.24 (3.8-4.7)	0.19 (0.1-0.3)
NT-proBNP PF/S	≤ 1.48	0.539 (0.479-0.597)	94.1 (85.6-98.4)	29.6 (23.7-36.1)	44.3 (38.2-47.1)	1.34 (1.1-1.7)	0.20 (0.08-0.5)
Light criteria	3 CRIT	0.896 (0.860-0.925) <sup>a</sup>	71.4 (31-80.4)	90.2 (86.1-93.4)	85.6 (82.5-89.1)	7.27 (6.3-8.3)	0.32 (0.2-0.5)
Cholesterol PF, (mg/dL)	≤ 57	0.894 (0.859-0.923)	94.7 (88.0-98.3)	81.0 (76.1-85.3)	83.7 (79.2-85.9)	4.98 (4.6-5.4)	0.07 (0.03-0.2)
Albumin gradient (g/L)	> 1.4	0.829 (0.787-0.865) <sup>b</sup>	76.1 (66.1-84.4)	80.4 (75.3-84.9)	80.2 (76.1-84.5)	3.89 (3.4-4.4)	0.3 (0.2-0.5)

LDH PF ≤ 2/3 of the normal upper limit of LDH in serum (the three criteria should be met); LDH PF/S ratio ≤ 0.6; Light criteria for pleural transudate: NLR: negative likelihood ratio; NT-proBNP: N-terminal pro-brain natriuretic peptide; PF: pleural fluid; PF/S protein ratio ≤ 0.5; PLR: positive likelihood ratio; S: serum.

<sup>a</sup>Not significant compared with PF cholesterol.<sup>b</sup>p < 0.011 compared with PF cholesterol (95% confidence interval).

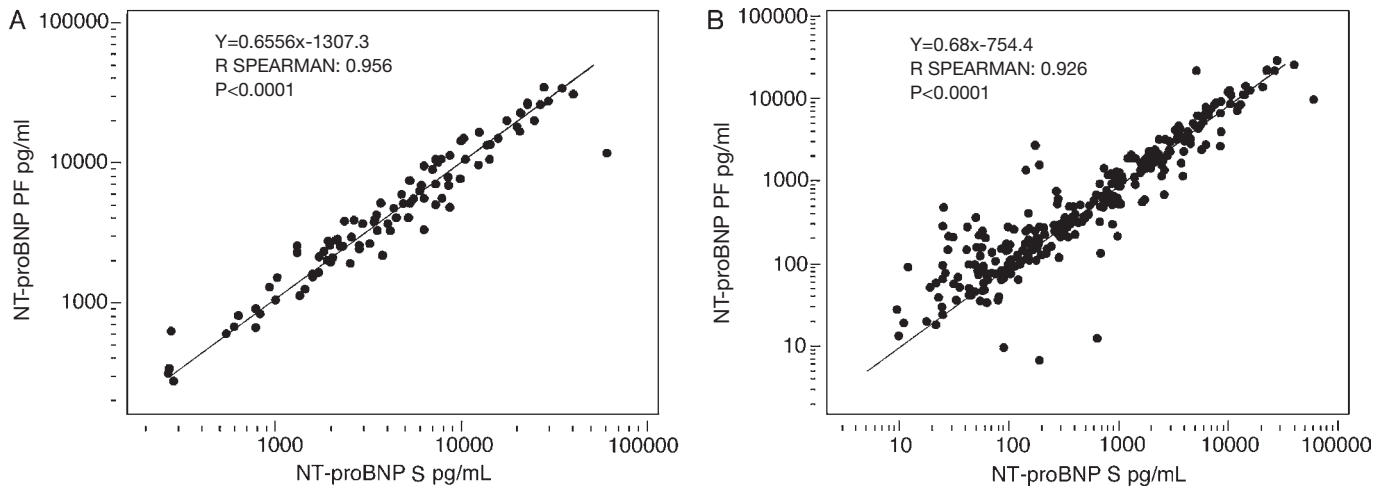
It does not seem that the method for determining the levels of NT-proBNP influences these results as it was similar in the majority of the studies. In our opinion, the difference in the results can be due to the sample size (in general, previous studies included few patients), to the large variability of NT-proBNP (whose values are modified by multiple factors, such as age, sex, anemia, body mass or cardiac dysfunction)<sup>25-28</sup> and the type of patients included. In this sense, there are studies that only included transudates of cardiac origin,<sup>12,14,16</sup> while others also incorporated patients with transudates of other etiologies.<sup>11,15,17,18</sup> In these, NT-proBNP was able to better discriminate

between both types of transudates, capability that neither the Light criteria nor CHOL PF possess. When the series only includes cardiogenic transudates, effectiveness, at least in theory, would be equal. Another aspect to consider is the number of exudates included compared with the number of transudates of cardiac origin. While in some studies they are at least 50% of the series,<sup>15,18</sup> in others they are 26.8%,<sup>14</sup> which is similar to our study (23.6%). NT-proBNP PF classifies better pleural effusions of cardiac origin (14.9% errors) than exudates (20.3% of errors) and it therefore seems logical to think that the higher the percentage of exudates that are included, the poorer the

**Figure 2.** A) values of NT-proBNP in pleural fluid and B) values of NT-proBNP in serum in the six groups of patients studied for the diagnosis of pleural effusions of cardiac origin.

NPE: neoplastic pleural effusion; PPE: parapneumonic pleural effusion; TBPE: tuberculous pleural effusion; NT-proBNP: N-terminal pro-brain natriuretic peptide; CO: cardiac origin; OE: other exudates; OT: other transudates

The scale is logarithmic.



**Figure 3.** A) correlation of the levels of NT-proBNP in serum (S) and pleural fluid (PF) in the effusions of cardiac origin, and B) in all the pleural effusions studied. The scale is logarithmic; y = NT-proBNP PF; x = NT-proBNP S.

**Table 4**

Percentage of misclassified effusions in each group, for each parameter studied and for the diagnosis of pleural effusions of cardiac origin

	NT-proBNP S (%)	NT-proBNP PF (%)	NT-proBNP PF/S (%)	Light criteria (%)	CHOL PF (%)	Albumin gradient (%)
CHF	10.3	14.9	5.9	28.6	5.3	21.7
OT	30	7.7	80	75	100	63.6
NPE	26	19.4	79.2	7.2	24	15.2
PPE	41.9	24.6	74.4	9.4	15.1	29.6
TBPE	9.1	10	42.4	4	8	8.3
OE	30	25	71.7	6.8	11	17.6
Total	23.7	18.6	55.7	14.4	16.3	19.8
p <sup>a</sup>	0.011	NS	< 0.0001		NS	0.0402
p <sup>b</sup>	0.0268	NS	< 0.0001	NS		NS

CHF: congestive heart failure; CHOL: cholesterol; LDH PF/S  $\leq$  0.6; Light criteria for pleural transudates: LDH PF  $\leq$  2/3 of the upper limit of normal of LDH in serum (the three criteria should be met); NPE: neoplastic pleural effusion; NS: not significant; NT-proBNP: N-terminal pro-brain natriuretic peptide; OE: other exudates; OT: other transudates; PF: pleural fluid; PF/S protein ratio  $\leq$  0.5; PPE: parapneumonic pleural effusion; TBPE: tuberculo pleural effusion; S: serum.

<sup>a</sup>In comparison with the Light criteria.

<sup>b</sup>In comparison with the CHOL PF.

diagnostic effectiveness reached. In addition, age and sex are factors that influence the levels of NT-proBNP, which tend to be higher in women and the elderly.<sup>23</sup> It is striking that the Light criteria were one of the parameters with greater diagnostic effectiveness when they mistakenly classified 28.6% of effusions secondary to CHF. This could be due to the high number of exudates included in our series (73.1%), as these criteria had been designed to diagnose this type of pleuritis.

The diagnostic efficacy of NT-proBNP in our study was similar in S and in PF, in agreement with what has been previously published,<sup>14,15</sup> while the NT-proBNP PF/S ratio was very low (specificity 29.6%, diagnostic precision 44.3%). CHOL PF better diagnoses pleural

effusion of cardiac origin (sensitivity 94.7%: 89/94), although it is not able to differentiate between these and other types of transudates. In addition, this parameter also better classifies pleural transudates (sensitivity 95.3%: 102/107). It would therefore be an inverse situation of the Light criteria: the fewer the number of exudates included in the study, the greater the diagnostic efficacy reached. The combination of NT-proBNP PF (with a cut-point of 276 pg/mL in order to obtain a sensitivity of 100%) and CHOL PF, is what diagnoses a greater number of effusion of cardiac origin.

A limitation of our study is that, in excluding pleural effusions of unknown causes, it is possible that the results obtained could be overestimated. The number of patients excluded, for this reason as

**Table 5**

Results obtained with the determination of the N-terminal pro-brain natriuretic peptide fragment in pleural fluid in previous studies for the diagnosis of pleural effusions of cardiac origin

Reference	n	CHF	OT	Exudates	Cut-point	AUC	S (%)	Sp (%)	PLR	NLR
Porcel et al <sup>11</sup>	117	44	10	63	1,500 (pg/mL)	0.97	91	93	13	
Tomcsányi et al <sup>12</sup>	28	14	0	14	599-1,457 (pg/mL)	1	100	100		
Kolditz et al <sup>14</sup>	93	25	0	68	4,000 (ng/L)	0.98	92	93		
Porcel et al <sup>15</sup>	93	53	5	35	1,500 (pg/mL)	0.93	92	87	7.4	
Liao et al <sup>16</sup>	40	10	0	30	2,220 (pg/mL)	0.99	100	96.7		
Han et al <sup>17</sup>	240	82	16	142	1,714 (pg/mL)	0.99	99	99		
Porcel et al <sup>18</sup>	181	90	10	81	1,300 (pg/mL)	0.96	95.6	87.9	7.9	0.05
Valdés et al	398	94	13	291	1,409 (pg/mL)	0.89	85.1	79.9	4.24	0.19

AUC: area under the curve; CHF: congestive heart failure; NLR: negative likelihood ratio; OT: other transudates; PF: pleural fluid; PLR: positive likelihood ratio; S: sensitivity; Sp: specificity.

well as for presenting two possible causes for the pleural effusion, is within the usual range in these cases.<sup>29</sup> As it would not be practical in daily clinical practice, we have not taken into account the previous use of diuretics or those circumstances that can influence in the values of NT-proBNP,<sup>25-28</sup> fundamentally age and sex as, on one hand, mean NT-proBNP values in subjects over the age of 65 is 1.5 times higher than in younger subjects<sup>30</sup> and, on the other mean NT-proBNP values in women are between 2 and 4 times greater than in men for the same age group.<sup>25</sup>

In conclusion, the determinations of NT-proBNP, in PF as well as in S, for the diagnosis of pleural effusions of cardiac origin, are not superior to those of CHOL PF and the Light criteria. This latter, could be favored in our study due to the high number exudates in our series. The combination of NT-proBNP PF and CHOL PF is that which better diagnoses pleural effusions of cardiac origin. Given these results and the influence of multiple factors that modify the levels of NT-proBNP, we cannot recommend at this time the inclusion of these parameters among the determinations in routine daily practice. Nevertheless, they could be useful in those cases in which the origin of the effusion has yet to be defined and there is suspicion that it may be due to CHF.

### Conflict de Interest

The authors declare having no conflict of interest.

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