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ORIGINAL ARTICLE

Solving the Light's criteria misclassification rate of cardiac and hepatic transudates

SILVIA BIELSA,[1]* JOSÉ M. PORCEL,[1]* JOSÉ CASTELLOTE,[3] ESTELA MAS,[1] AURELI ESQUERDA [2] AND RICHARD W. LIGHT[4]

Departments of [1]Internal Medicine and [2]Laboratory Medicine, Pleural Diseases Unit, Arnau de Vilanova University Hospital, Biomedical Research Institute of Lleida, Lleida, [3]Department of Gastroenterology, Hepatology and Liver Transplant Unit, Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain, and [4]Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

ABSTRACT

Background and objective: **Pleural transudates are most commonly due to heart failure (HF) or hepatic hydrothorax (HH), but a number of these effusions are misclassified as exudates by standard (Light's) criteria. The aim of this study was to determine the prevalence of mislabelled transudates and to establish simple alternative parameters to correctly identify them.**

Methods: **We retrospectively analysed the pleural fluid and serum protein, lactate dehydrogenase and albumin concentrations from 364 cardiac effusions and 102 HH. The serum–to–pleural fluid protein and albumin gradients (serum concentration minus pleural fluid concentration), as well as the pleural fluid–to–serum albumin ratio (pleural fluid concentration divided by the serum concentration) were calculated for the mislabelled transudates.**

Results: **Light's criteria had misclassified more HF-associated effusions than HH (29% vs 18%, $P = 0.002$). A serum–to–pleural fluid protein gradient >3.1 g/dL correctly identified 55% and 61% of the HF and HH false exudates, respectively. The figures for an albumin gradient >1.2 g/dL were 83% and 62%. Finally, a pleural fluid–to–serum albumin ratio <0.6 had identical accuracy for labelling miscategorized cardiac and liver-related effusions (78% and 77%, respectively).**

Conclusions: **If the clinical picture is consistent with HF but the pleural fluid meets Light's exudative criteria, the measurement of the albumin rather than the protein gradient is recommended. In the context of cirrhosis, a potentially 'false' exudate is identified better by the pleural fluid–to–serum albumin ratio.**

SUMMARY AT A GLANCE

Contrary to common belief, the albumin gradient performs significantly better than the protein gradient to correctly classify 'false' exudates of cardiac origin. In contrast, in patients with cirrhosis whose pleural fluid meets Light's exudative criteria, the use of the albumin ratio is preferred.

Key words: albumin gradient, exudate, hepatic hydrothorax, pleural effusion, transudate.

INTRODUCTION

The most common cause of transudative effusions is heart failure (HF), followed by hepatic hydrothorax (HH).[1] The latter complicates cirrhosis in about 5–10% of the cases.[2] HH probably results from the passage of ascites to the pleural cavity through diaphragmatic defects and, therefore, the composition of the pleural fluid mirrors that of the peritoneal fluid.[2]

Even though HF and HH are typically transudates, they can be misclassified as exudates by Light's criteria.[1] It has been demonstrated that 20–30% of HF-associated pleural fluids meet exudative criteria.[3] One study showed that pleural fluid constituents (protein, albumin, lactate dehydrogenase (LDH) and their fluid/serum ratios) became progressively more concentrated over time, thus giving rise to false-positive exudates in HF patients receiving diuretics.[4] In this specific clinical context, examination of the albumin or protein gradients (serum minus pleural fluid values) has been recommended.[5] Some experts favour the use of the protein gradient because pleural fluid and serum protein concentrations should have already been available for the application of Light's criteria.[4,5] However, due to the small numbers of

Correspondence: José M. Porcel, Department of Internal Medicine, Arnau de Vilanova University Hospital, Avda Alcalde Rovira Roure 80, 25198 Lleida, Spain. Email: jporcelp@yahoo.es

*Both authors contributed equally.

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patients studied and reported in the literature, a firm recommendation cannot be made.

The misclassification rate of cirrhosis-associated effusions is also not known. The percentage of transudates in six studies, totalling 110 HH, varied between 75% and 94%.[6–11] None reported the albumin gradient or ratio for the mislabelled transudates, except for Gurung *et al.*[6] who showed an albumin gradient >1.2 g/L in one of two HH false exudates.

The aims of this study were to ascertain the prevalence of false exudates in a large series of patients with HF and HH, and to determine whether the protein gradient, albumin gradient or the pleural–to–serum albumin ratio best establishes their true transudative nature.

METHODS

Patients

We retrospectively reviewed all consecutive patients with HH and HF who underwent a diagnostic thoracentesis at the Arnau de Vilanova University Hospital (Lleida, Spain) from 1995 to 2011. The patients had been admitted to hospital because of decompensated HF or major complications of cirrhosis. Due to the low prevalence of HH, the series was completed by 44 additional HH patients recruited for 3 consecutive years from the Bellvitge University Hospital (Barcelona, Spain). Demographical, clinical and analytical (protein, LDH, and albumin in the pleural fluid and serum) data were recorded. The use of diuretics before thoracentesis could only be reliably registered in HH patients. It should be noted that in our laboratory, pleural fluid protein concentrations are routinely performed on all fluid specimens, whereas the albumin levels are only measured following specific physician request. The study was approved by the hospital ethics committee of the participant centres (CEIC no. 972).

Diagnostic criteria

The diagnosis of HF was based on history, physical examination, chest radiographs, electrocardiogram or echocardiogram, and on response to diuretic therapy. HH was defined as a pleural effusion in a cirrhotic patient without any underlying cardiorespiratory, infectious or malignant disease. Criteria for transudates required the exclusion of any disease associated with exudative effusions (e.g. malignancy, infection, tuberculosis, pericardial diseases, pulmonary embolism, surgery, trauma, autoimmune systemic diseases), and 3 or more months of patient observation in order to confirm resolution of the effusion with diuretic therapy.

Pleural fluid measurements

Aspirated pleural fluid was collected into 5-mL sterile heparinized tubes for biochemical and, when necessary, microbiological and cytological analyses. Biochemical measurements were carried out immediately after thoracentesis on discrete analysers (Hitachi 717 and 911, or Hitachi Modular DP, Roche Diagnostic, Mannheim, Germany) using standardized methods.

Light's criteria for separating transudates from exudates were applied to all HF and cirrhosis-associated effusions.[1] The protein and albumin gradients (serum minus pleural fluid), as well as the pleural–to–serum albumin ratio (pleural fluid divided by serum) were also calculated. The serum sample was obtained within the 24 hours of the pleural tap. The upper normal limit for LDH serum level was 480 U/L and 750 U/L in Lleida and Barcelona medical centres, respectively. Thus, pleural fluid LDH values less than 320 U/L and 500 U/L, respectively, were indicative of transudates.

Statistical analysis

Demographics and laboratory variables were expressed as medians and interquartile ranges. Between-group comparisons of quantitative and qualitative variables were performed with the Fisher's exact and Mann–Whitney *U* tests, respectively. According to previous reports, the adopted cut-off points to identify transudates for the albumin gradient, protein gradient and the albumin ratio were 1.2 g/dL, 3.1 g/dL and 0.6, respectively.[4,12,13] The statistical significance level was set at 0.05 (two-tailed). All analyses were conducted using statistical software SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Patients' characteristics

Database review initially identified 457 patients with the clinical diagnosis of HF-related and 125 with HH-related effusions. Ninety-three and 23 patients, respectively, were excluded from the analysis because the necessary data for the application of Light's criteria were missing. Thus, the study population comprised 364 patients with HF and 102 with HH, whose baseline characteristics are listed in Table 1. Ninety-five per cent of patients with HH were receiving diuretic therapy at the time of thoracentesis. Patients with HH were younger, and their serum albumin levels were lower than those with cardiac effusions (2.9 vs 3.5 g/dL, $P < 0.01$). Similarly, the pleural fluid protein and albumin levels were significantly lower in the cirrhotic group.

Prevalence of transudates by Light's criteria and protein/albumin gradients

Light's criteria correctly classified more HH- (82%) than HF-associated effusions (71%, $P = 0.02$) (Table 2). The pleural fluid LDH level <2/3 of upper

Table 1 Baseline characteristics of patients

Data	Heart failure ($n = 364$)	Hepatic hydrothorax† ($n = 58$)	Hepatic hydrothorax‡ ($n = 44$)	P§
Age, years	79 (73–84)	69 (56–76)	63 (51–67)	<0.01
Male gender	188 (52)	42 (72)	19 (43)	0.13
Serum:				
Protein, g/dL	6.3 (5.8–6.8)	6.4 (5.9–7)	6.2 (5.4–6.5)	0.62
Albumin, g/dL	3.5 (3.2–3.8)	2.9 (2.4–3)	2.6 (2.4–2.9)	<0.01
LDH, U/L¶	386 (330–468)	399 (318–461)	790 (554–908)	0.00
Pleural fluid:				
Protein, g/dL	2.4 (1.7–2.9)	1.2 (0.9–2.1)	1.5 (0.8–2.5)	<0.01
Albumin, g/dL	1.4 (1–1.7)	0.7 (0.5–1)	0.8 (0.5–1.4)	<0.01
LDH, U/L	164 (129–216)	119 (94–158)	270 (154–382)	0.43

Data are expressed as medians (interquartile range) or number (%).
† Patients from Arnau de Vilanova University Hospital.
‡ Patients from Bellvitge University Hospital.
§ For comparisons between heart failure and the sum of hepatic hydrothoraces from both centres.
¶ The upper limit of normal for the serum LDH was 480 U/L in one centre and 750 U/L in the other.
LDH, lactate dehydrogenase.

Table 2 Identification of transudates by Light's criteria and other parameters

Parameter	Heart failure		Hepatic hydrothorax		P
	No.	Sensitivity, % (95% CI)	No.	Sensitivity, % (95% CI)	
Transudative Light's criteria	364	71 (66–75)	102	82 (74–89)	0.02
PF/serum protein <0.5	364	82 (78–85)	102	91 (84–95)	0.03
PF/serum LDH <0.6	364	81 (77–85)	102	85 (77–91)	0.35
PF LDH <2/3 of upper limits of normal	364	93 (89–95)	102	95 (89–98)	0.37
Serum-PF protein gradient >3.1 g/dL	364	82 (78–85)	102	93 (87–97)	0.01
Serum-PF albumin gradient >1.2 g/dL	133	95 (91–98)	76	86 (76–92)	0.01
PF/serum albumin ratio <0.6	133	94 (89–97)	76	95 (87–98)	0.82
Combined criteria					
PF/serum protein or PF LDH criteria	364	77 (73–81)	102	89 (82–94)	0.01
Protein or albumin gradient	133	100 (97–100)	76	99 (93–100)	0.19
Light's criteria or protein gradient	362	71 (66–75)	102	82 (74–89)	0.02
Light's criteria or albumin gradient	293	88 (83–91)	97	87 (78–92)	0.77
Light's criteria or albumin ratio	293	97 (95–99)	97	97 (91–99)	0.85

LDH, lactate dehydrogenase; PF, pleural fluid.

limits of normal represented the single parameter from Light's triad that fulfilled the largest number of HH and HF patients (95% and 93% respectively). As shown in Table 2, an albumin gradient above 1.2 g/dL was more useful in identifying HF than HH (95% vs 86%, $P = 0.01$), while the converse was true for a protein gradient higher than 3.1 g/dL (82% vs 93%, $P = 0.01$).

Mislabelled transudates

More than half of the misclassified transudates met only one of Light's three criteria for exudates and just by a small margin because their values were close to the established binary cut-offs (Table 3). The pleural fluid–to–serum protein was below 0.5 in 38% and 50% of miscategorized HF and HH, respectively. The respective figures for the pleural fluid–to–serum LDH lower than 0.6 were 36% and 17%, while those for the pleural fluid LDH less than two thirds of upper limits of normal were 75% and 72%.

Of 36 HF effusions misclassified as exudates by Light's criteria, 30 (83%) had an albumin gradient higher than 1.2 g/dL (Fig. 1). In contrast, this parameter only identified 8 of 13 (62%, $P = 0.1$) incorrectly categorized HH (Fig. 2). Moreover, 59 of 107 (55%) and 11 of 18 (61%, $P = 0.7$) false exudates caused by HF and cirrhosis, respectively, exhibited a protein gradient greater than 3.1 g/dL. Lastly, an albumin ratio lower than 0.6 was equally effective for the correct identification of HF (78%) and HH (77%, $P = 0.9$) mislabelled transudates (Figs 1,2).

Table 3 Light's criteria in the misclassified transudates

Parameter	Heart failure ($n = 107$)	Hepatic hydrothorax ($n = 18$)
Light's criteria		
PF/serum protein	0.51 (0.44–0.57)	0.48 (0.32–0.57)
PF/serum LDH	0.63 (0.56–0.75)	0.82 (0.69–0.96)
PF LDH	246 (194–312)	234 (135–388)[†] 440 (379–617)[‡]
No. of exudative Light's criteria met by the fluid	*n* (%)	*n* (%)
One	62 (58)	10 (55)
Two	37 (35)	5 (28)
Three	8 (7)	3 (17)

Data are expressed as median (interquartile range) or number (%), as appropriate.
[†] Patients from Arnau de Vilanova University Hospital.
[‡] Patients from Bellvitge University Hospital.
LDH, lactate dehydrogenase; PF, pleural fluid.

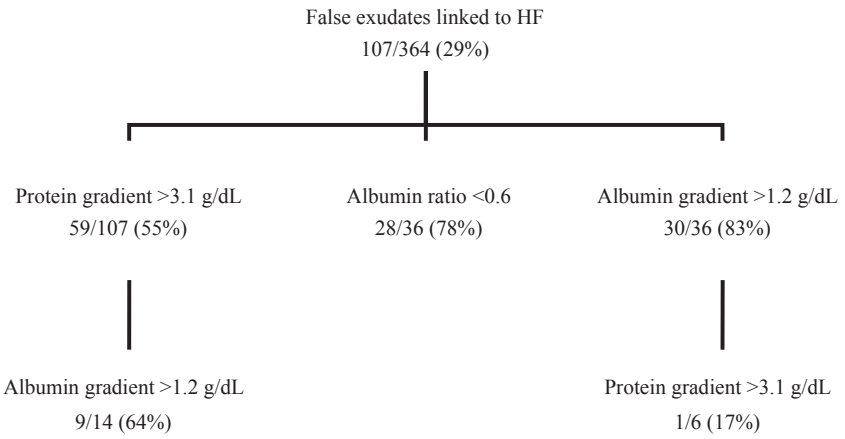

Figure 1 Mislabelled cardiac effusions. This flow chart represents the sequential application of different criteria in patients with misclassified cardiac effusions for whom data was available. HF, heart failure.

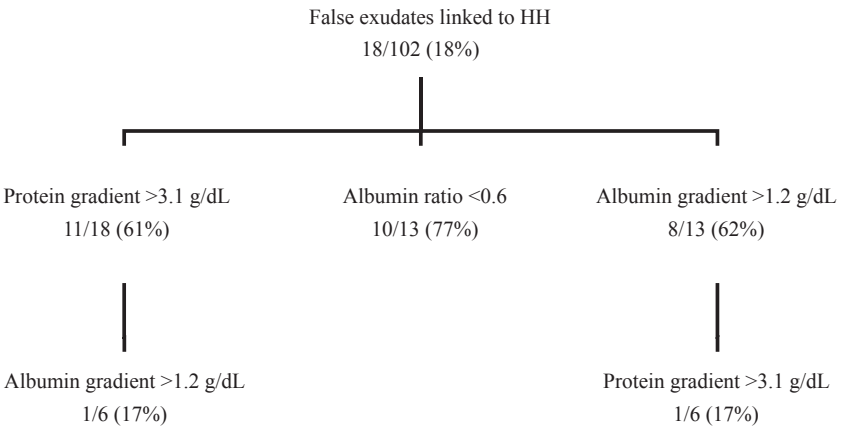

Figure 2 Mislabelled cirrhosis-associated effusions. This flow chart represents the sequential application of different criteria in patients with misclassified cirrhosis-associated effusions for whom data was available. HH, hepatic hydrothorax.

DISCUSSION

In a large number of patients with a cardiac or hepatic cause of pleural effusion, mislabelled transudates that meet exudative criteria are less common in the setting of cirrhosis (18%) compared with HF (29%). A pleural fluid–to–serum albumin ratio <0.6 and an albumin gradient >1.2 g/dL allowed correct identification of a significant proportion of effusions in the respective groups.

In about 25% of cases, patients with HF present with an exudative effusion in the absence of a cause

other than cardiac disease itself.[3] Most of these 'false' exudative effusions occur in those either receiving diuretic therapy or having bloody effusions. Romero-Candeira *et al*. performed serial thoracenteses at 48-hour intervals in 21 patients with HF-associated effusions who were given diuretics.[4] At subsequent procedures, pleural fluid protein and LDH concentrations increased by 43% and 67%, respectively, resulting in an increase in the number of false exudates. On the other hand, another study found that the specificity of Light's criteria for identifying exudates dropped from 81% in patients with pleural fluid erythrocyte counts $\leq 10\,000 \times 10^6$/L to 61% in those with higher red blood cell counts.[14] Misclassification was due to a change in the pleural fluid LDH values and/or the pleural fluid–to–serum LDH ratios.

Classically, protein or albumin gradients have been recommended for patients with mislabelled cardiac effusions,[5] but whether both offer similar discriminative properties is not known. In six previous reports, totalling 391 transudative effusions (about 5% of cirrhotic origin), investigators found a 28.5% rate of false exudates, of which 70% and 84% would have been correctly labelled by the application of the protein and albumin gradients, respectively.[11–13,15–17] Adding the current series would change these percentages to 62% and 80.5%, thus favouring the use of the albumin instead of the protein gradient (Table 4). For the albumin ratio, 23 of 26 (88%) misclassified transudates by Light's criteria showed a value below 0.6 in one study.[13] In the present investigation, this parameter also proved to be clinically helpful, particularly in the cirrhotic group.

Despite the use of diuretics being as common in HH as in HF patients, the frequency of misclassified effusions was significantly lower in the context of cirrhosis. Our results indicate that the albumin gradient was significantly better in HF than in HH miscategorized patients, while the albumin ratio was a relatively good parameter in both diseases. The probable underlying reason is that serum and pleural fluid albumin concentrations were lower in cirrhosis than in HF, and therefore, after the subtraction process, the remainder would more infrequently exceed 1.2 g/dL in the former. However, a ratio is less dependent on the absolute numbers when both the numerator and denominator decrease; it explains the better discriminatory characteristics of the albumin ratio in cirrhosis.

In recent years, natriuretic peptides have proven to be a useful adjunctive tool to discriminate between HF-related effusions and non-cardiac effusions, including HH.[18] N-terminal pro-B-type natriuretic peptide levels greater than 1300 pg/mL in either the serum or the pleural fluid are virtually diagnostic of HF.[18] Interestingly, in a composite of three studies from a single centre, 87% and 53% of 31 misclassified cardiac effusions had pleural N-terminal pro-B-type natriuretic peptide and protein gradients above the established diagnostic cut-offs for HF, respectively, whereas the albumin gradient would have correctly labelled 11 of 14 (79%) of these effusions.[19] The best test is not yet determined, and routine use of N-terminal pro-B-type natriuretic peptide awaits further studies.

This study has limitations. Its retrospective nature explains the lack of albumin gradient data in 63% and 25% of the misclassified HF and HH, respectively. It is plausible that clinicians ordered albumin measurements in pleural fluid and serum because they either thought the patients could have had a misclassified transudate (e.g. previous or current use of diuretics), or else, they already knew that Light's criteria had resulted in misclassification.

In conclusion, 18% of HH effusions are misclassified as exudates according to Light's criteria. However, in this clinical scenario, a pleural fluid–to–serum albumin ratio less than 0.6 is in favour of a transudate. For misclassified cardiac effusions, the albumin gradient or measurement of natriuretic peptides should be considered.

Table 4 Published reports examining misclassified transudates

Study	No. of transudates/HF/HH	Misclassified transudates by Light criteria, No. (%)	Misclassified transudates with protein gradient >3.1 g/dL, No. (%)	Misclassified transudates with albumin gradient >1.2 g/dL, No. (%)
Roth *et al*.[12]	18/15/1	5 (28)	ND	5 (100)
Akkurt *et al*.[15]	27/24/0	5 (19)	ND	5 (100)†
Burgess *et al*.[16]	123/84/ND	19/112 (17)	ND	13 (68)
Gonlugur *et al*.[13]	71/62/0	28 (39)	20/26 (78)‡	25/26 (96)
Han *et al*.[11]	98/82/16	32 (33)	18/28 (64)§	ND
Bayram *et al*.[17]	54/51/2	19 (37)§	13 (68)§	14 (74)§
Current series	466/364/102	125/466 (27)	70/123 (57)	37/49 (76)
Total	857/682/121	233/846 (27.5)	121/196 (62)	99/123 (80.5)

† Albumin gradient >1.4 g/dL.
‡ Protein gradient >3.0 g/dL.
§ Data from cardiac effusions.
HF, heart failure; HH, hepatic hydrothorax; ND, not done.

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