CHEST

Original Research

DISORDERS OF THE PLEURA

Improving the Predictive Accuracy of Identifying Exudative Effusions

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Background: **Application of Light's criteria results in misclassification of some transudative effusions as exudative, particularly because of congestive heart failure (CHF). We sought to determine if the serum to pleural fluid albumin (SF-A) and serum to pleural fluid protein (SF-P) gradients increased the predictive accuracy to correctly identify exudative effusions.**

Methods: **We retrospectively analyzed 1,153 consecutive patients who underwent a diagnostic thoracentesis at the Medical University South Carolina. Univariable logistic regression analyses were used to determine the statistical significance of pleural fluid tests that correctly identified exudative effusions. Tests with significant diagnostic accuracy were combined in multivariable logistic regression models, with calculation of areas under the curve (AUCs) to determine their predictive accuracy. The predictive capability of the best model was compared with Light's criteria and other test combinations.**

Results: **Pleural fluid lactate dehydrogenase (LDH), SF-A gradient, and SF-P gradient had a significant effect on the probability of identifying exudative pleural effusions. When combined together in a multivariable logistic regression, LDH (OR, 14.09 [95% CI, 2.25-85.50]), SF-A gradient (OR, 7.16 [95% CI, 1.24-41.43]), and SF-P gradient (OR, 6.83 [95% CI, 1.56-27.88]) had an AUC of 0.92 (95% CI, 0.85-0.98).**

Conclusions: **Application of Light's criteria, not uncommonly, misclassifies CHF transudative effusions as exudates. In cases where no cause for an exudative effusion can be identified or CHF is suspected, the sequential application of the fluid LDH, followed by the SF-P and then the SF-A gradients, may assist in reclassifying pleural effusions as transudates.**

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Abbreviations: CHF = congestive heart failure; FL-R = pleural fluid to serum lactate dehydrogenase ratio; FP-R = pleural fluid to serum protein ratio; LDH = lactate dehydrogenase; SF-A = serum to pleural fluid albumin; SF-P = serum to pleural fluid protein; UNL = upper normal limit

Pleural effusions are identified as either exudative or transudative by using Light's criteria.[1] The sensitivity of Light's criteria for exudative effusions is 99%, but the specificity ranges from 65% to 85%.[2] As a result, some transudative effusions are misclassified as exudative, particularly those due to congestive heart failure (CHF) when diuretics are given.

Other pleural fluid tests and test combinations have been described.[3-13] When compared with Light's criteria, the majority of these pleural fluid tests and test combinations have maintained comparable sensitivities but failed to increase specificity for correctly

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identifying exudative effusions. Bayesian analysis to overcome misclassification of transudative effusions as exudative was also proposed.[14,15] However, another study showed that Bayesian analysis marginally improved the correct identification of exudative effusions.[16]

Another proposed method to reduce the misclassification of transudative effusions as exudative is the use of the serum to pleural fluid albumin (SF-A) and serum to pleural fluid protein (SF-P) gradients. In one study, an SF-A and SF-P gradient > 1.2 g/dL and 3.1 g/dL, respectively, correctly identified 86% and 91% of the transudates.[17] Light's criteria correctly identified only 75% of those transudates.[17] In another study, the SF-A and SF-P gradients correctly identified 83% and 55% of misclassified transudates due to CHF, respectively.[18]

The use of albumin and protein gradients appears to reduce the misclassification of transudative effusions as exudative, particularly those related to CHF. Therefore, a stepwise approach combining the use of Light's criteria with the albumin and protein gradients to correctly identify exudative effusions seems logical. We sought to determine if SF-A and SF-P gradients increased the predictive accuracy to correctly identify exudative effusions.

Materials and Methods

We retrospectively reviewed all consecutive patients who underwent a diagnostic thoracentesis at Medical University of South Carolina (Charleston, South Carolina) from 1999 until 2011. Clinical characteristics collected included age; sex; cause of the pleural effusion; serum protein, lactate dehydrogenase (LDH), and albumin concentrations; and the following pleural fluid tests: pH, protein, LDH, cholesterol, and albumin. Serum protein, LDH, albumin, and pleural fluid tests were performed in an analyzer using standard technology (UniCel DxC 800; Beckman Coulter, Inc). Pleural fluid pH was collected using heparinized syringes and transported in ice to the laboratory, where it was processed within 1 h after collection in a blood gas machine (ABL 800FLEX; Radiometer Medical ApS). The study protocol was approved by the Institutional Review Board for Human Research at Medical University of South Carolina (protocol number 00016055). Criteria used to establish the cause of an effusion is described in detail in e-Appendix 1.

Light's criteria, which combine a pleural fluid to serum protein ratio (FP-R) > 0.5, a fluid to serum LDH ratio (FL-R) > 0.6 or the upper normal limit (UNL) serum LDH as triplets with an "or" rule, were applied to all effusions. The UNL serum LDH in our laboratory was 240 IU/L. Therefore, two-thirds UNL for serum LDH corresponded to a value of 160 IU/L. Modified Light's criteria, defined as pleural fluid LDH > 0.45 UNL of serum (corresponding to a value of 108 IU/L) in combination with FP-R > 0.5 or FL-R > 0.6 as triplets with an "or" rule, were also applied to all effusions.[6] An effusion with either a fluid LDH > 160 IU/L or a fluid cholesterol > 45 mg/dL combined in pair with an "or" rule, was considered exudative. Misclassified transudative effusions by Light's criteria were then reclassified by applying the SF-A gradient, SF-P gradient, and SF-A ratio using previously defined cutoff values.[6,17] Final consensus of the diagnosis for each pleural effusion was established by three of the authors.

Statistical Analysis

We examined the discriminative properties of eight pleural fluid tests: pH, total protein, LDH, cholesterol, FP-R, FL-R, SF-A gradient, and SF-P gradient. Cutoff points to identify exudative effusions were obtained for all eight tests from previously reported and defined cutoff values.[6,17] Sensitivities, specificities, and likelihood ratios (positive and negative) with 95% CI for all eight pleural fluid tests were calculated. Because not every patient had all eight pleural fluid tests available, the size of the datasets used to generate each of the discriminative properties varied. A two-tailed P value of ≤ .05 was considered significant. Means (95% CI) and medians (interquartile range) were used to compute the descriptive statistics for transudates and exudates. A two-tailed t test or its nonparametric alternative, Wilcoxon rank-sum, were used to test the differences of pleural fluid tests between transudates and exudates. All hypotheses were tested at a Bonferroni adjusted two-sided α level of 0.00625 (0.05/8).

Univariable and multivariable logistic regression analyses were applied to individual pleural fluid tests as well as test combinations with equal or better diagnostic performance characteristics than Light's criteria (ie, higher specificity). The area under the curve was then calculated for individual pleural fluid tests that showed statistical significance. These tests were combined and compared with Light's criteria and other test combinations to determine if they increased the predictive accuracy to correctly identify exudative effusions. When analyzed by multivariable logistic regression, the pleural fluid tests not included by Light's criteria (pleural fluid pH, cholesterol, SF-A gradient, and SF-P gradient) that showed statistical significance were sequentially added to those tests already included by Light's criteria (FP-R, FL-R, and two-thirds UNL of LDH) that also showed statistical significance using an "or" rule. Internal validation of the final model was assessed using bootstrap analysis. Bootstrapping is the preferred method quantifying the uncertainty of the model, when this has already been decided.[19] Compared with cross-validation, bootstrapping tends to drastically reduce the variability of the estimates by randomly selecting subsamples with replacement from the original data set. In our analysis, we used a total of 200 subsamples and averaged the results over 100 repetitions. All analyses were carried out using SAS, version 9.2 (SAS Institute Inc) software.

Results

Approximately two-thirds of a total of 1,153 patients (67%) examined in our registry had exudates (Table 1). Exudates had significantly lower fluid pH and higher fluid protein, LDH, and cholesterol levels (Table 2). The FP-R and FL-R were significantly higher among exudates. The SF-A and SF-P gradients were significantly lower among exudates. Except for the pleural fluid pH, the sensitivities of the eight pleural fluid tests were similar (Table 3). Sensitivities were also similar between Light's criteria, modified Light's criteria, and two-test combination LDH and cholesterol. No single test or combination was superior.

There were seven pleural fluid tests with similar or better specificity than Light's criteria: (1) pH < 7.30, (2) protein, (3) LDH, (4) cholesterol, (5) FP-R, (6) FL-R, and (7) SF-P gradient. When tested in a univariable logistic regression, five tests showed a significant effect on the probability of correctly identifying exudates: (1) pleural