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Differential Diagnosis of Pleural Effusion by Lactate Dehydrogenase Isoenzyme Analysis*

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Study objective: **To determine the diagnostic value of pleural fluid lactate dehydrogenase (LDH) isoenzyme analysis in the differential diagnosis of pleural fluid.**
Patients and methods: **Eighty-seven consecutive patients with pleural effusion caused by congestive heart failure (33), infection (33), and malignancy (21) comprised a derivation set of patients. Pleural fluid LDH activity and isoenzyme pattern were established in all patients and analyzed by the classification and regression trees (CART) method. An additional group of 20 consecutive patients comprised a validation set that was used for cross-validation of CART-derived decision tree.**
Results: **A decision tree, with a positive predictive value of 83%, was constructed and validated by data from a validation set of patients.**
Conclusions: **Pleural fluid LDH isoenzyme pattern may be helpful for the differential diagnosis of the most common causes of pleural effusions: congestive heart failure, infections, and malignancy.** ***(CHEST 1997; 111:648-51)***

Key words: CART; isoenzymes; lactate dehydrogenase; pleural effusion

Abbreviations: CART=classification and regression trees; CHF=congestive heart failure; LDH=lactate dehydrogenase

Pleural effusions can present a challenging diagnostic problem. The differential diagnosis is diverse, but most common causes include congestive heart failure (CHF), malignancy, and pneumonia-related effusion. Studies on pleural fluid yield a definitive or presumptive diagnosis in about 74% of cases.[1] Measurements of pleural fluid lactate dehydrogenase (LDH) levels are useful as one of the parameters in the separation of exudative from transudative effusions.[2] The value of pleural fluid LDH isoenzyme patterns is controversial.[3-5] Based on the determination of total and isoenzyme electrophoretic pattern of LDH, we report an algorithm useful for the differentiation among malignant, infectious, and CHF etiologies of pleural effusion.

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Materials and Methods

The usefulness of the pleural LDH isoenzyme pattern was determined from a derivation set of patients and then tested in a validation set.

Derivation Set

Pleural fluid was collected from 87 consecutive patients with pleural effusion caused by CHF (33 patients), pneumonia (parapneumonic, 18; empyema, 15), and malignancy (lung carcinoma, 8; lung metastases, 10; lymphoma, 3). The effusion was attributed to CHF if the patient, known to suffer from heart failure, had a long-standing effusion (≥1 month) with normal results of microbiologic and cytologic studies, was afebrile, and did not have evidence of acute thoracic or abdominal infection, autoimmune disease, hypothyroidism, or cancer. Since long-standing pleural effusion due to CHF may have either transudative or exudative parameters,[6] the criteria of Light et al[2] for the diagnostic separation of transudates and exudates were not required for diagnosis of pleural fluid caused by CHF. Malignant effusion was defined as effusion with malignant cells or when due to atelectasis or mediastinal lymphadenopathy in association with histologically proved primary or metastatic lung disease. Pneumonia-related effusions included empyema and parapneumonic effusions. None of the patients with pneumonia-related effusions had a history of CHF. Owing to group size, patients with pulmonary embolism, autoimmune diseases, active tuberculosis, portal hypertension with ascites, and posttraumatic effusion were excluded from the study. The categorization of patients into the

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diagnostic groups was performed without knowledge of the LDH isoenzyme results. In patients with effusion attributed to pneumonia and malignancy, pleural fluid analysis was performed before any therapy. LDH isoenzymes were determined by an LDH isoenzyme electrophoresis kit (P/N 655940; Beckman Instruments; Fullerton, Calif) and expressed as a percentage of the total LDH activity. Normal serum range of LDH activities is 100 to 300 U.

Validation Set

Results of LDH isoenzymes in pleural effusion obtained from patients in this set were used for testing the quality of prediction of the decision tree. The validation set was composed of 20 patients with pleural effusion due to CHF (three), malignancy (eight), and pulmonary infections (nine). Definition and exclusion criteria were identical to those of the derivation set.

Sequential Evaluation of LDH Isoenzyme Pattern

In six patients from the derivation set with long-standing pleural effusions, more than one evaluation of pleural fluid was performed. Only the first LDH isoenzyme pattern was considered for construction of the classification and regression tree (CART) algorithm. The sequential LDH isoenzyme patterns over time were analyzed in relation to changes in the etiology of pleural effusion.

Data Analysis and Statistics

We used classification and regression trees,[7] henceforth referred to as CART. CART is a nonparametric method that aims to obtain subsets of the data that are more similar with respect to the diagnosis. The subsets are created using the proportions of LDH isoenzymes and the total LDH levels. CART builds a binary decision tree structure in which at each joint it splits the data into two sets according to LDH levels. The splits, *ie*, at which joint to split according to which LDH variable and at what level, are determined so that the patient's diagnosis at resulting end nodes would be the most similar compared with all the other possible splits. For example, at the beginning, all the levels of LDH-1 are determined, and the data broken into two subsets according to each specific split. For each split, the program obtains the overall gini index of diversity, where each node has its own mean of LDH-1. This determines the measure of "goodness" of a split. When all such splits and their measure of goodness have been computed, the split that finds the greatest diversity is chosen. This procedure is repeated recursively until either the gini index is zero or there are no more than five observations at a node. This step determines the full tree.

A full tree is equivalent to a saturated model. As such it may not generalize well, as it fits the specific sample too closely. The second step in CART is to "prune," *ie*, delete some of the later splits. This step is done by comparing the combined increased similarity of diagnosis of the specific node from which they all stem. The increase in measure of similarity is counterweighed by the number of nodes added to the tree. In this way, the more efficient splits remain in the decision tree. CART considers only nested subtrees formed by pruning at different reweighing levels.

In our study, the tree was grown and pruned on the full derivation set. An additional validation set was then tested for obtaining measures of predictive accuracy. A positive predictive value of the validation set is given with a confidence interval of 95%.

RESULTS

Derivation Set

Total LDH and LDH isoenzymes of malignant, CHF, and pneumonia-related effusions are presented in Table 1. Results of the pleural fluid CART are presented in Figure 1. Overall, the decision tree had a positive predictive value of 83%. Sensitivity, specificity, and positive predictive value for the specific diagnostic categories are presented in Table 2. Malignant pleural effusions had two different LDH isoenzyme patterns. Positive pleural fluid cytology did not distinguish between the two LDH isoenzyme patterns.

Validation Set

The CART algorithm correctly predicted the diagnosis of pleural effusion in 17 of 20 patients in the validation set (positive predictive value, 85%; confidence interval, 84.4 to 85.6%). These results are similar to the positive predictive value observed in the derivation set of patients. The algorithm correctly diagnosed all pneumonia-related effusions but misdiagnosed the nature of pleural fluid in two patients with malignancy (suggesting CHF) and one with CHF (suggesting malignancy).

Sequential Evaluation of LDH Isoenzymes in Chronic Pleural Effusion

Overall, six patients with CHF had more than one evaluation of LDH isoenzyme patterns. Only the first LDH isoenzyme pattern was considered for construction of the decision tree in the derivation set. In four of the six patients, CHF remained the

Table 1—*LDH Values* in Pleural Effusions According to Etiology*

Diagnosis	Total LDH, U	LDH Isoenzymes, %				
		1	2	3	4	5
CHF (n=33)	137.7±93.7	21.8±10.8	34.2±8.9	16.0±6.7	11.3±6.9	16.8±9.8
Pneumonia (n=33)	3576.7±7195.3	6.0±4.3	14.4±6.9	15.0±4.3	21.3±6.0	43.3±10.9
Malignancy (n=21)	1790.8±5524.0	11.1±8.1	30.0±15.1	17.3±5.5	15.3±8.6	26.2±15.4

*Values are mean±SD.

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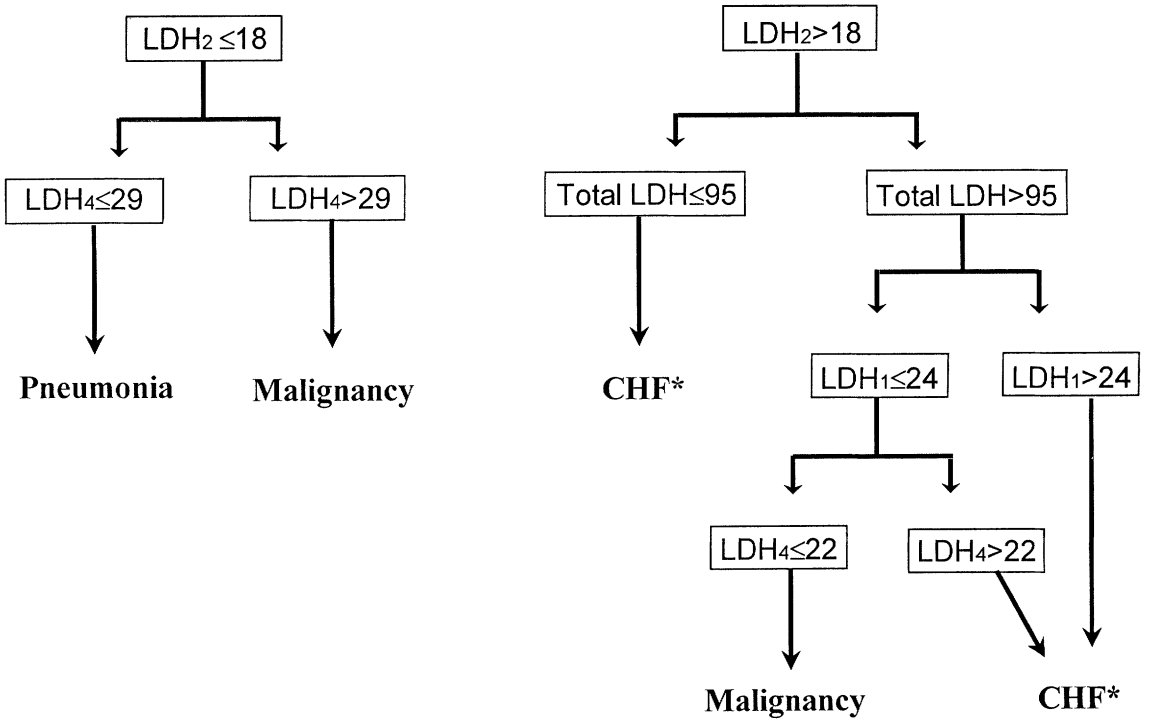

FIGURE 1. Classification and regression tree for pleural effusion analysis based on total and isoenzyme pattern of LDH measurements. Total LDH activity is expressed in units (normal serum is 100 to 300 U). LDH isoenzymes are expressed as relative percentage of total LDH. Asterisk indicates congestive heart failure.

only cause for persistent pleural effusion and no change in the LDH isoenzyme pattern was observed. In two patients with an initial clinical diagnosis of CHF and compatible LDH isoenzymes, pneumonia developed. A second LDH isoenzyme analysis at the time of pneumonia was consistent with pneumonia-related effusion. Repeated determinations of LDH isoenzymes following resolution of pneumonia (following 4 and 5 weeks, respectively) demonstrated a return in pleural LDH isoenzymes to a pattern compatible with CHF.

DISCUSSION

LDH, a tetrameric protein composed of four monomers, is expressed as five isoenzymes, having different distribution in various tissues. Serum LDH isoenzymes may be useful in disease diagnosis[8] since tissue damage releases isoenzymes contained therein, leading to a change in their pattern. It has been shown that pleural LDH isoenzyme pattern differs from that in serum.[9] The present study demonstrates that analysis of pleural LDH isoenzyme pattern may be helpful in diagnosing the cause of pleural effusion. By application of the CART method, a decision tree with a positive predictive value of 83% was established and reconfirmed by a validation set of patients.

LDH isoenzyme analysis, which requires small volume samples, is quick and easy to perform. The decision tree can be applied at the patient's bedside. The commonly used criteria of Light et al[2] for the differentiation of pleural effusion establish the exudative or transudative nature of the pleural fluid but do not determine its specific etiology. In contrast, our decision tree enables a specific diagnosis of the most common causes of pleural effusion: CHF, malignancy, and pneumonia.

Previous studies of the diagnostic utility of pleural LDH isoenzyme patterns reported controversial results.[3-5] Several studies describe relative values of LDH isoenzymes in different pathologic states, without the application of statistical methods, concluding

Table 2—*Sensitivity, Specificity, and Positive Predictive Value of LDH Isoenzyme Decision Tree

Diagnosis	Sensitivity, %	Specificity, %	Positive Predictive Value, %
CHF	79	98	96
Infection	88	93	88
Malignancy	81	85	63

*The sensitivity, specificity, and positive predictive values were derived from the derivation set of patients.

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that pleural LDH isoenzymes are not diagnostic.[3,4] The failure of these descriptive studies to demonstrate the utility of LDH isoenzymes in the diagnosis of pleural fluids may arise from our finding that the categories of pleural fluid etiologies did not have a single LDH isoenzyme pattern. In contrast, Vergnon et al[5] reported five different pleural fluid isoenzyme patterns that were characteristic but not pathognomonic for different causes of pleural effusion. However, the bedside application of their computerized classification is cumbersome.

In our study, there was more than one LDH isoenzyme pattern in the malignancy-associated effusions. This could be due to the various neoplastic tissues that secrete different LDH isoenzymes. It has been shown that malignant lymphomas and small cell lung carcinoma differ from other malignancies by a low LDH-5 isoenzyme secretion.[5] Alternatively, the extent of the pleural inflammatory response to malignancy and the variable degree of pleural polymorphonuclear leukocytosis may determine the relative levels of LDH-4 and LDH-5 isoenzymes.[5] A marked heterogeneity of malignant etiologies and a relatively small number of malignant pleural effusions in the present study precluded separation between two LDH isoenzyme patterns according to the cytopathologic diagnosis.

Cytology is considered the gold standard for the diagnosis of malignant pleural effusions. Pleural fluids frequently contain few morphologically recognizable malignant cells so that even the most experienced cytologists are unable to render a definitive diagnosis. In the present study, cytologic examination of the pleural fluid was positive in seven (33%) and four (50%) of malignant effusions in the derivation and validation sets, respectively. LDH isoenzyme pattern correctly predicted malignancy in 9 of 11 patients with cytologically positive malignant effusions and in 15 patients (83%) with malignancy and cytologically negative effusions. Therefore, LDH isoenzyme analysis may contribute to cytologic evaluation of pleural fluid and may suggest a malignant etiology even in cytologically negative neoplastic pleural effusions.

Sequential repeated evaluation of pleural fluid showed no change in LDH isoenzyme pattern when the cause of the fluid was not changed. However, in two cases of chronic pleural effusion with superimposed pneumonia, an appropriate change in LDH isoenzyme occurred. This suggests that a change in the LDH isoenzyme pattern over time should lead to a search of additional explanations for pleural fluid accumulation.

We have limited our initial investigation, due to sample size, to three of the most common causes of pleural effusion. The presented decision tree may be useful for the differentiation of pleural effusion caused by pneumonia, CHF, and malignancy. However, owing to the relatively small study population, further studies are indicated to confirm the utility of this decision tree for these as well as the less common etiologic categories.

In summary, we have shown that pleural fluid LDH isoenzyme pattern may be useful in the differential diagnosis of pleural effusion when the diagnostic possibilities are limited to malignancy, pneumonia-related effusion, and CHF.

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