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Official publication of the American College of Chest Physicians



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*Chest* 2002;121:1916-1920  
DOI 10.1378/chest.121.6.1916

The online version of this article, along with updated information and services can be found online on the World Wide Web at:  
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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S<sup>®</sup>

# Multilevel Likelihood Ratios for Identifying Exudative Pleural Effusions\*

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**Study objectives:** To determine multilevel likelihood ratios for pleural fluid tests that are commonly used to discriminate between exudative and transudative pleural effusions.

**Design:** Meta-analysis of patient-level data.

**Patient data:** Selected studies included patients with diagnoses of exudative or transudative pleural effusions who underwent thoracentesis and laboratory analysis of their pleural fluid.

**Measurements and methods:** Studies were identified by searching MEDLINE and related bibliographies. Data were obtained for 1,448 patients from seven primary investigators or extracted from dot plots in published reports. Likelihood ratios were calculated from extracted data stratified across ranges of test result values.

**Results:** Sufficient data were available to calculate multilevel likelihood ratios for the elements of Light's criteria (pleural fluid lactate dehydrogenase [LDH], ratio of pleural fluid to serum LDH, and ratio of pleural fluid to serum protein), pleural fluid protein, ratio of pleural fluid to serum cholesterol, pleural fluid cholesterol, and gradient of pleural fluid to serum albumin. Each of these tests provided levels of likelihood ratios through the most clinically relevant range (0 to 10).

**Conclusion:** Multilevel likelihood ratios combined with a clinician's estimation of the pretest probability of an exudative effusion improve the diagnostic accuracy of discriminating between exudative and transudative pleural effusions. Likelihood ratios avoid the use of confusing terms, such as "pseudoexudates," that derive from the use of single cutoff points for pleural fluid tests.

(CHEST 2002; 121:1916-1920)

**Key words:** body fluids; pleura; pleural disease; pleural effusion; thoracentesis

**Abbreviations:** LDH = lactate dehydrogenase; LDH-PF = pleural fluid lactate dehydrogenase expressed as a fraction of the upper limits of normal for the serum assay; LDH-R = ratio of pleural fluid to serum lactate dehydrogenase

Pleural effusions of uncertain etiology are extremely common diagnostic challenges that warrant thoracentesis and pleural fluid analysis to categorize the effusion as an exudate or transudate. Because exudative effusions present a broad differential diagnosis of various inflammatory and malignant conditions that often require additional diagnostic or therapeutic interventions,<sup>1</sup> accurate categorization of an effusion is fundamentally important.

Multiple investigations have examined the discriminative properties of different pleural fluid tests for identifying exudative effusions.<sup>2-10</sup> These studies

usually compare the operating characteristics of individual tests among patients with different etiologies of pleural effusions in order to identify tests with the highest sensitivity and specificity. Established clinical practice has favored diagnostic strategies that combine pleural fluid lactate dehydrogenase (LDH), the ratio of pleural fluid to serum LDH (LDH-R), and the ratio of pleural fluid to serum protein combined in "or" rules (Light's criteria),<sup>2</sup> wherein an exudative effusion is identified if any one of the criteria is fulfilled. More recent studies have examined the diagnostic utility of pleural fluid cholesterol,<sup>3-7</sup> bilirubin,<sup>8,10</sup> and albumin<sup>8,9</sup> concentrations comparing the sensitivities and specificities of the new tests with the three-test combination of Light's criteria.

Unfortunately, these studies and expert opinion recommend a single cutoff point to dichotomize pleural effusions into transudative or exudative categories. This approach loses much of the diagnostic information contained in laboratory tests that have continuous integer values.<sup>11-13</sup> Moreover, recom-

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Work performed at the Medical University of South Carolina. Manuscript received August 13, 2001; revision accepted December 5, 2001.

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recommendations for the use of test combinations in “or” rules increase the sensitivity but decrease the specificity of the pleural fluid analysis for identifying exudates.<sup>12</sup> This increased sensitivity is intended to avoid false-negative results when evaluating patients with exudative effusions, which have greater diagnostic import than transudative effusions. The lower specificity, however, has resulted in the coinage of the confusing term “pseudoexudates” for effusions in patients who appear clinically unlikely to have an exudative effusion but fulfill diagnostic criteria for an exudative effusion on pleural fluid analysis.<sup>14</sup>

An alternative strategy for improving the discriminative properties of diagnostic tests is to generate multilevel likelihood ratios using cutoff points and apply these ratios to convert pretest probability to posttest probability of an exudative effusion.<sup>13</sup> With this strategy, laboratory results in the borderline exudative range with the use of single cutoff points generate low likelihood ratios that would not misclassify patients if the pretest suspicion for an exudative effusion were low.

We previously reported the results of a meta-analysis<sup>15</sup> using discrete, patient-level data previously reported in primary studies to compare the operating characteristics of different pleural fluid tests for identifying exudative effusions. We have reanalyzed these data to generate likelihood ratios for pleural fluid exudates across the range of results for commonly used pleural fluid tests. These analyses allow a Bayesian approach to diagnosis that improves the accuracy of pleural fluid categorization and avoids subcategories of effusions, such as pseudoexudates.

## MATERIALS AND METHODS

The literature search and collection of data from primary investigators were previously reported.<sup>15</sup> Briefly, a MEDLINE search and a search of the investigators’ files retrieved articles published since 1976 that reported the operating characteristics of tests that discriminated between exudative and transudative effusions. Primary investigators were contacted and asked to provide their primary data in spreadsheet format. Data were accepted into the analysis if two examiners determined that: (1) data points were available from the primary investigators or could be extracted from dot plots in the original reports, (2) discrete data points could be linked to individual patients, and (3) an acceptable reference standard was used to categorize the patients’ effusions as exudates or transudates.

Data were pooled into statistical software (JMP; SAS Institute; Cary, NC) that grouped patients into exudative and transudative categories subgrouped by discrete strata of test result ranges. Cutoff points for the test result strata were selected to provide multiple likelihood ratios within their most clinically useful range from 0 to 10. Test result strata that did not contain test values for patients with transudative effusions were reported as “noncalculable” because the resultant likelihood ratio calculations would require division by zero. These values were estimated from a prediction equation derived from linear regression with natural log transformation of the calculable likelihood ratios.

Likelihood ratios were calculated by standard methods.<sup>13</sup> The study received an exemption from institutional review board approval.

## RESULTS

As previously reported,<sup>15</sup> 11 studies<sup>3–10,14,16,17</sup> were identified in the literature, of which 4 studies containing 408 patients<sup>10,14,16,17</sup> were excluded because original data were no longer available or because investigators did not enroll consecutive patients. The remaining seven studies<sup>3–9</sup> provided data on 1,448 patients and eight pleural fluid tests, which included pleural fluid protein (1,187 patients), ratio of pleural fluid to serum protein (1,393 patients), pleural fluid LDH expressed as a fraction of the upper limits of normal for the serum assay (LDH-PF) [1,438 patients], LDH-R (1,388 patients), pleural fluid cholesterol (1,248 patients), the ratio of pleural fluid to serum cholesterol (1,123 patients), and the gradient of serum to pleural fluid albumin (386 patients). The ratio of pleural fluid to serum bilirubin (303 patients) was also available in the data set, but these data were not examined in this study because of their previously reported poor discriminative properties.<sup>15</sup>

The patients’ underlying diagnoses have been previously reported<sup>15</sup> and are shown in Table 1. Seventy-four percent of the effusions were exudates, and 26% were transudates. Likelihood ratios calculated from the

**Table 1—Clinical Features of the Study Population\***

Variables	Data
Age, yr	54.6 ± 20.5
Male gender, No. (%)	744 (54.5)
Female gender, No. (%)	620 (45.5)
Transudates	377
Congestive heart failure	270
Cirrhosis	43
Nephrosis	39
Hypoalbuminemia	25
Exudates	1,071
Malignancy	438
Tuberculosis	296
Infection	185
Miscellaneous	73
Pulmonary embolism	36
Collagen vascular disease	17
Trauma	14
Pancreatitis	5
Postpericardiotomy syndrome	4
Pleuropericarditis	1
Vasculitis	1
Yellow nail syndrome	1
Total effusions	1,448

\*Data are presented as mean ± SD or No. unless otherwise indicated.

primary data are shown in Tables 2–5, along with the numbers of patients in each stratum of test results.

## DISCUSSION

The medical literature commonly describes the operating characteristics of a diagnostic test by dichotomizing test results into normal and abnormal values and calculating the sensitivity and specificity of the test.<sup>18</sup> Unfortunately, knowledge of the sensitivity and specificity of a test offers little clinical utility when evaluating individual patients because these indexes do not describe the probability of disease if the test result is positive.<sup>19</sup> Dichotomization of test results treats borderline abnormal and extreme test results the same and ignores important clinical information.<sup>11,13,15</sup> Moreover, test dichotomization does not assist in assessing to what degree a test result alters a clinician's estimation of the pretest probability of disease.

Likelihood ratios more accurately convey how a specific test result identifies the target disorder by quantifying the likelihood of a given test result in patients with a condition compared with the likelihood of the same result in patients without the condition.<sup>13,18</sup> Likelihood ratios also have advantages over the indexes of positive and negative predictive values because these latter values depend on the prevalence of the target condition in the population

**Table 2—Likelihood Ratios for Pleural Fluid Protein and of Pleural Fluid to Serum Protein Ratios**

Variables	Exudates, No.	Transudates, No.	Likelihood Ratio
Pleural fluid protein, g/dL			
> 5.0	265	2	47.25
4.6–5.0	184	2	32.80
4.1–4.5	138	3	16.40
3.6–4.0	120	18	2.38
3.1–3.5	66	23	1.02
2.6–3.0	51	35	0.52
2.1–2.5	21	42	0.18
1.6–2.0	18	88	0.07
≤ 1.5	12	99	0.04
Ratio of pleural fluid to serum protein			
> 0.70	475	1	168.65
0.66–0.70	150	1	53.26
0.61–0.65	117	6	6.92
0.56–0.60	102	12	3.02
0.51–0.55	70	14	1.78
0.46–0.50	47	34	0.49
0.41–0.45	27	34	0.28
0.36–0.40	13	37	0.12
0.31–0.35	8	44	0.06
≤ 0.30	19	182	0.04

**Table 3—Likelihood Ratios for LDH-PF and LDH-R Ratios**

Variables	Exudates, No.	Transudates, No.	Likelihood Ratio
LDH-PF			
> 1.00	626	5	44.33
0.91–1.00	57	2	10.09
0.81–0.90	43	7	2.17
0.71–0.80	61	6	3.60
0.61–0.70	78	13	2.12
0.51–0.60	56	31	0.64
0.41–0.50	59	49	0.43
0.31–0.40	54	73	0.26
0.21–0.30	18	97	0.07
≤ 0.20	10	93	0.04
LDH-R			
> 1.10	657	6	38.92
1.01–1.10	47	1	16.71
0.91–1.00	50	3	5.92
0.81–0.90	56	10	1.99
0.71–0.80	64	17	1.34
0.61–0.70	50	18	0.99
0.51–0.60	34	26	0.46
0.41–0.50	27	54	0.18
0.31–0.40	21	94	0.08
≤ 0.30	18	135	0.05

being tested. Our study reports the multilevel likelihood ratios for the commonly performed tests that discriminate between transudative and exudative pleural effusions.

To our knowledge, the data set from which the likelihood ratios were calculated is the largest available, being collected from the primary investigators who provided discrete patient-level test results. Large sample sizes enhance the accuracy of likelihood ratio estimates.<sup>13,18</sup> All of the commonly used tests evaluated in this study provide likelihood ratios that extend beyond the most clinically useful range of 0 to 10. This finding supports the conclusion that each of these tests provides comparable diagnostic information when used in a single test strategy.<sup>15</sup>

Clinical practice and expert opinion have established Light's criteria as the "gold standard" for discriminating between exudative and transudative pleural effusions.<sup>20,21</sup> This three-test combination has been stated to have a lower specificity as compared with the use of more recently recommended single tests, such as pleural fluid cholesterol.<sup>22,23</sup> The lower specificity of Light's criteria,<sup>2</sup> however, is an expected consequence of combining multiple tests in a parallel manner using an "or" rule in an effort to enhance sensitivity.<sup>12</sup> Moreover, two of the components of Light's criteria—pleural fluid LDH and LDH-R—demonstrate multicollinearity (Pearson coefficient of correlation = 0.84) in the data of the present study,<sup>15</sup> and would not be expected to

**Table 4—Likelihood Ratios for Pleural Fluid Cholesterol and Pleural Fluid to Serum Cholesterol Ratios\***

Variables	Exudates, No.	Transudates, No.	Likelihood Ratio
Pleural fluid cholesterol, mg/dL			
> 90	395	1	106.49
81–90	138	3	12.40
71–80	122	5	6.58
61–70	109	8	3.67
51–60	81	17	1.28
41–50	64	43	0.40
31–40	40	63	0.17
21–30	22	86	0.07
11–20	0	1	0.00
≤ 10	12	38	0.09
Ratio of pleural fluid to serum cholesterol			
> 0.55	390	3	44.42
0.51–0.55	92	2	15.72
0.46–0.50	89	0	NC 7.22†
0.41–0.45	86	8	3.67
0.36–0.40	58	14	1.42
0.31–0.35	52	23	0.77
0.26–0.30	32	41	0.27
0.21–0.25	12	37	0.11
0.16–0.20	8	49	0.06
0.11–0.15	6	56	0.04
0.05–0.10	4	33	0.04
≤ 0.05	8	20	0.14

\*NC = noncalculable values.

†Estimated value from linear regression.

perform well when combined in a diagnostic test model.<sup>24</sup> This multicollinearity results from the inclusion of LDH-PF as one of the terms in the calculation of LDH-R (LDH-PF/serum LDH). Likelihood ratios allow sequential application of tests avoiding the loss of specificity when tests are combined in a dichotomous manner with “or” rules.

The likelihood ratios from the present study climbed to > 1, indicating an increased probability of an exudate, at the previously reported cutoff points for each of the examined pleural fluid tests

**Table 5—Likelihood Ratios for Pleural Fluid to Serum Albumin Gradient**

Albumin Gradients, g/dL	Exudates, No.	Transudates, No.	Likelihood Ratio
≤ 0.8	146	1	74.86
0.9–1.0	23	1	11.79
1.1–1.2	36	3	6.15
1.3–1.4	14	20	0.36
1.5–1.6	7	13	0.28
1.7–1.8	3	19	0.08
1.9–2.0	3	13	0.12
> 2.0	4	51	0.04

from this data set,<sup>15</sup> with the exception of LDH-PF. In the present study, the likelihood ratio rose to > 1 at an LDH-PF range of 0.61 to 0.70, which differs from the cutoff point of 0.45 we previously reported.<sup>15</sup> Our previous report<sup>15</sup> selected cutoff points that maximized sensitivity while maintaining the highest diagnostic accuracy for the tests. LDH-PF represents a special case, however, because of its multicollinearity with LDH-R.<sup>15</sup> Because of this multicollinearity, the cutoff point for LDH-PF that produced the highest sensitivity and overall diagnostic accuracy when combined with the other two tests in Light’s criteria was 0.45, even though a cutoff point of 0.67 performed better when LDH-PF was considered by itself.

On the basis of our findings, how should patients with pleural effusions be evaluated? Clinicians first estimate the probability of an exudative effusion on the basis of their knowledge of a patient’s clinical presentation.<sup>11</sup> This pretest probability is converted to pretest odds by the following equation: probability/(1 – probability). The pretest odds is then multiplied by the likelihood ratio, which generates the posttest odds. The posttest odds is then converted to the posttest probability by the following equation: posttest odds/(posttest odds + 1). Likelihood ratio normograms are available to quickly convert pretest to posttest probabilities at the bedside.<sup>11</sup> If the posttest probability is diagnostically indeterminate with a midrange value, it can be treated as a new “pretest” probability, converted to pretest odds, and multiplied by a likelihood ratio from the results of a second pleural fluid test. This calculation generates a new posttest odds, which can be converted to a posttest probability. A clinical example using serial likelihood ratios is shown in Table 6.

A limitation of the study derived from our efforts to partition the sample into multiple levels so as to provide clinically useful likelihood ratios. This resulted in a small number of patients in several of the test result levels. Absence of patients with transudative effusions within a test result level results in a noncalculable likelihood ratio because of the need to divide by 0. These values, however, were estimated by a nonlinear regression analysis of the other likelihood ratios for that test. The small number of values within some extreme test result levels caused several calculated likelihood ratios to fall out of the expected integer series. As shown in Table 5, for instance, albumin gradient values between 0.19 to 0.20 had a higher likelihood ratio than albumin gradient values between 0.17 to 0.18. Any inaccuracies in calculated likelihood ratios at these extreme ranges of test result values, however, would not affect posttest odds to a clinically important degree because of the low values of the likelihood ratios.

The study results are also limited by weaknesses in

**Table 6—Serial Use of Likelihood Ratios to Categorize a Pleural Effusion\***

Pleural fluid results
Pleural fluid to serum protein ratio = 0.45
Pleural fluid LDH (fraction of laboratory normal) = 0.65
Pleural fluid to serum LDH ratio = 0.75
Light's criteria <sup>23</sup>
Pleural fluid to serum protein ratio > 0.5, or
Pleural fluid LDH (fraction of laboratory normal) > 0.67, or
Pleural fluid to serum LDH ratio > 0.6
Calculation of posttest probability
Pretest probability of an exudate = 20%
Pretest odds = pretest probability/(1.00 - pretest probability) = 0.20/(1.00 - 0.20) = 0.25
Pleural fluid protein ratio LR = 0.49 (Table 2)
Posttest odds <sub>1</sub> = pretest odds × LR = 0.25 × 0.49 = 0.12
Pleural fluid LDH = 2.12 (Table 3)
Posttest odds <sub>2</sub> = 0.12 × 2.12 = 0.25
LDH-R LR = 1.34 (Table 3)
Posttest odds <sub>3</sub> = 0.25 × 1.34 = 0.34
Posttest probability of an exudate = posttest probability/(1.00 + posttest probability) = 0.34/(1.00 + 0.34) = 0.25 = 25%

\*LR = likelihood ratio. A patient with congestive heart failure and a pleural effusion underwent diuresis for 1 week but the effusion did not resolve. Thoracentesis was performed with the results shown, and the fluid was categorized as an exudate by Light's criteria.<sup>23</sup> Because the clinicians had a low pretest suspicion of an exudate (20% pretest probability) in the setting of heart failure, they concluded that the effusion was a pseudoexudate due to diuresis of a congestive heart failure effusion. Serial use of likelihood ratios for each of Light's criteria,<sup>23</sup> however, calculated a low posttest probability (25%) for an exudate, supporting the clinical impression of a transudative effusion related to heart failure. The use of serial likelihood ratios prevented the use of the term "pseudoexudate." The terms odds<sub>1</sub>, odds<sub>2</sub>, and odds<sub>3</sub> indicate three different posttest odds.

the experimental designs of the primary studies that were reported in our original meta-analysis.<sup>15</sup> The results of the primary studies, however, are entrenched into clinical practice with the standard use of their proposed tests to discriminate between exudative and transudative effusions. The likelihood ratios proposed in this study present a more useful approach for using existing data until more rigorously designed studies are reported in the future.

In conclusion, aggregate data from our previous meta-analysis allow the calculation of multilevel likelihood ratios for pleural fluid tests used to discriminate between exudative and transudative pleural effusions. These likelihood ratios can be used in a Bayesian manner to estimate the posttest probability of an exudative effusion in a strategy that improves diagnostic accuracy and quantifies diagnostic confidence.

ACKNOWLEDGMENT: The authors thank the primary authors for providing their primary, patient-level data.

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