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Diagnostic Value of Lactate Dehydrogenase Isoenzyme Pattern in Pleural Effusions

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Summary: Lactate dehydrogenase isoenzymes have been used to classify the nature of pleural effusion. Nevertheless, studies have reported conflicting results. The objective of this study was to evaluate the diagnostic value of lactate dehydrogenase isoenzymes in the analysis of pleural effusions.

Pleural fluid samples obtained from three respective diagnostic groups: group I transudate (n = 23), group II parapneumonic effusion (n = 29) and group III malignant effusion or pleuritis carcinomatosa (n = 41) were evaluated.

Total lactate dehydrogenase activity and lactate dehydrogenase (LDH) isoenzyme pattern were significantly different between transudative (group I) and exudative (group II and III) effusions. Group II and III showed a low percentage of LDH1 ($p < 0.001$), whereas the percentages of LDH4 ($p < 0.001$) and LDH5 ($p < 0.001$) were higher compared to group I. Moreover, in exudative effusions the percentage of LDH1 ($p < 0.005$), LDH4 ($p < 0.005$), as well as LDH5 ($p < 0.005$) were significantly different between parapneumonic and malignant effusions. In contrast to relative lactate dehydrogenase isoenzyme values, the absolute values of lactate dehydrogenase isoenzymes did not differ between group II and group III. Logistic regression analysis yielded a strong discrimination between group I and II+III, simultaneously using lactate dehydrogenase, glucose and protein as explanatory variables. Logistic regression analysis yielded only a weak discrimination between group II and III, simultaneously using lactate dehydrogenase, glucose and the absolute values of LDH2 and LDH4 as explanatory variables.

In conclusion, the lactate dehydrogenase isoenzyme pattern differed between pleural effusions of transudative and exudative origin. However, including lactate dehydrogenase isoenzyme activities in the biochemical work-up of pleural effusions did not reveal an additional discriminatory value in the assessment of the classification of these effusions.

Introduction

Pleural effusions have classically been divided into transudates and exudates. The pleural fluid lactate dehydrogenase concentration has among others, been used in the analysis of pleural effusion, especially to discriminate transudates from exudates (1–6). However, total lactate dehydrogenase activity in the pleural fluid is of little value in the discrimination between various types of exudative effusions such as malignant from non-malignant effusions (1, 3–9). Cytoplasmic, cellular enzymes, such as lactate dehydrogenase in the extracellular space are suggestive indicators for disturbances of the cellular integrity induced by pathological conditions. As lactate dehydrogenase is present in essentially all major organ systems (10–12), lactate dehydrogenase measurement is a sensitive, but rather non-specific test. The concentration of the pleural fluid lactate dehydrogenase is a reliable indicator of pleural inflammation (14, 15). Even though the total pleural fluid lactate dehydrogenase activity is not useful in distinguishing among various exudative pleural effusions, one might suppose that lactate dehydrogenase isoenzymes could be of additional value in the differentiation (13). Only few studies report on the analysis of lactate dehydrogenase isoenzymes in pleural effusion and the results have been conflicting (9, 10, 16, 17).

The aim of this study was to evaluate the possible diagnostic value of lactate dehydrogenase isoenzymes in the analysis of pleural effusions, especially in the differentiation between parapneumonic (effusions caused by a pneumonic infection with negative bacterial cultures of the pleural effusion) and malignant effusions (effusions caused by malignant involvement of the pleura).

Materials and Methods

Patients

During a 2-year period, prospectively all patients referred to the pulmonary ward because pleural effusion diagnosis were studied

(n = 135; age 66.2 ± 14.9). For this study, only diagnostic thoracocenteses were considered, and, when more than one was performed only data of the first were studied.

Materials

On all pleural fluid samples, the following analyses were performed: glucose, protein, lactate dehydrogenase, lactate dehydrogenase isoenzymes, cell count, amylase, bacterial and fungal culture, acid-fast bacilli smear and culture and cytology. Simultaneously, a sample of serum was obtained to measure biochemical properties. The pleural effusions were individually classified in transudate (n = 23) or exudate (n = 112) after careful evaluation of all clinical and biochemical data with respect to the criteria of *Light* (15). According to *Light*, exudative pleural effusions meet at least one of the following criteria, whereas transudative effusions meet none:

1) pleural fluid protein divided by serum protein greater than 0.5
2) pleural fluid lactate dehydrogenase divided by serum lactate dehydrogenase greater than 0.6
3) pleural fluid lactate dehydrogenase greater than two-thirds the upper limit of normal for serum lactate dehydrogenase.

The following cases were excluded for this study: effusions of undetermined origin, effusions with more than one possible cause, empyemas, tuberculosis and haemothorax. Out of the exudate parapneumonic (n = 29) and malignant effusions (n = 41) were selected. The diagnosis was based on biochemical, cytologic and bacteriologic examination of the fluid. So, finally 93 cases were used for the present study. An effusion was considered parapneumnic when this effusion was associated with a pneumonia, pulmonary abscess, or bronchiectasis and when the pleural fluid demonstrated a predominance of polymorphonuclear leukocytes, but negative bacterial cultures. An effusion was considered malignant when malignant cells were demonstrated in the pleural fluid, pleural biopsy specimen, or at autopsy. Other causes of effusions were excluded.

Controls

A group of 48 healthy control subjects (age 58 ± 13 years) – without relevant medical history – was chosen to assess reference values of serum lactate dehydrogenase and its isoenzymes. Serum values of lactate dehydrogenase, γ-glutamyltransferase, alanine aminotransferase, creatine kinase, creatinine and protein were within normal ranges.

Methods

Laboratory tests

The pleural fluid was immediately centrifuged, or if necessary, stored at 4 °C and centrifuged within 2 hours at 1000 *g* for 5 minutes. The supernatant was collected and the lactate dehydrogenase activity was measured on a Beckman Synchron CX-7 system (testkit No 442660) according to the recommendations of the Deutsche Gesellschaft für Klinische Chemie [DGKC-recommendations]. The reference ranges for serum lactate dehydrogenase are 200–450 U/l. For the determination of the lactate dehydrogenase isoenzymes the Beckman Paragon Lactate Dehydrogenase Electrophorese's Kit was used (testkit No 655940, Beckman Instruments Inc, Mijdrecht, The Netherlands). Electrophoresis and scanning of the gels were performed with the Beckman Appraise System (Beckman Instruments Inc, Mijdrecht, The Netherlands).

Statistical methods

Data are expressed as mean ± SD. In order to detect statistically significant differences between the three patient groups, for each of the discriminatory variables separately, data were analyzed by the *Kruskal-Wallis* one-way analysis of variance (ANOVA) test. The *Mann-Whitney* U test was used for pairwise comparisons. Because 10 comparisons were made, a probability value smaller than 0.15/10 being 0.005 was considered statistically significant (*Bonferroni*'s correction).

Logistic regression analysis was used to test the discriminatory effect of explanatory variables simultaneously. Primary interest was to discriminate transudative effusion (group I) from parapneumonic effusion (group II) and malignant effusion (III) combined; second interest was to discriminate group II from group III. In these analyses likelihood ratios were used; variables with a significance larger than 10% were left out of the logistic regression models. The results are presented by means of log odds ratios, observed versus predicted group membership, and receiver operating characteristics curves (18). For discriminating lactate dehydrogenase group II from group III, predicted probabilities are calculated per quartile of one explanatory variable, adjusted for the other explanatory variables in the logistic regression model by putting them on their mean value (19).

Results

Of the 93 patients finally studied, 23 of the obtained pleural effusions were classified as transudates (group I), 29 as parapneumonic effusions (group II) and 41 as malignant effusions (group III). Some biochemical properties are detailed in table 1. Serum lactate dehydrogenase did not show statistically significant differences between the three groups. The pleural fluid lactate dehydrogenase isoenzymes in patients with transudative pleural effusions were similar to their serum isoenzyme pattern and not significantly different from a normal control group (tabs. 1 and 2). The pleural fluid to serum lactate dehydrogenase activity ratio was 0.35 ± 0.09 in group I, 3.40 ± 5.38 in group II, and 3.40 ± 6.38 in group III. The mean pleural fluid lactate dehydrogenase isoenzyme percentages are shown in table 1. The mean percentage LDH1 was significantly higher in group I as compared to both group II ($p < 0.005$) and III ($p < 0.005$), as well as group II compared to group III ($p < 0.005$). The mean percentage LDH4, as well as LDH5 were significantly higher in group III as compared to both group II ($p < 0.005$) and I ($p < 0.001$), as well as group III compared to group II ($p < 0.005$). The mean pleural fluid lactate dehydrogenase isoenzyme absolute concentrations showed statistically significant differences only between the transudative effusions (group I) and the exudative effusions (group II and III), but not between group II and III, respectively.

As it can be seen from tables 3 and 4 and figure 1, logistic regression analysis yielded a strong discrimination between group I and group II plus III combined, given three independent variables simultaneously used in the model: lactate dehydrogenase, glucose and protein. All other independent variables were far from being significant when added to the model (p-values well beyond 0.10). Between group II and III only a weak discrimination was found, given the variables lactate dehydrogenase, glucose, and the absolute values of LDH2 and LDH4 (see tabs. 5 and 6 and fig. 1); all other independent variables were far from being significant when added to the model (p-values well beyond 0.10). It has

Tab. 1 Biochemical characteristics and lactate dehydrogenase (LDH) isoenzymes in pleural effusions obtained from the studied groups, as well as in serum obtained from a healthy control group.

	n	Leukocytes (10^9/l)	Glucose (mmol/l)	Protein (g/l)	LDH (U/l)	LDH1 (%)	LDH2 (%)	LDH3 (%)	LDH4 (%)	LDH5 (%)
Controls[a]	48				361 ± 54 362 (219–475)	21.2 ± 3.4 20.9 (14–27.7)	39.7 ± 2.5 40.4 (33.8–44.1)	18.6 ± 1.9 18.7 (13.8–23.2)	8.7 ± 1.4 8.7 (6.2–11.5)	11.8 ± 3.2 11.7 (3.6–23.3)
Transudative effusion (I)	23	1.07 ± 1.66*+ 0.6 (0.1–7.5)	7.5 ± 1.8* 7.2 (5.4–12.3)	19.5 ± 7.2++ 19.7 (6.9–32.4)	164 ± 41**++ 178 (43–233)	33.6 ± 20.0**++ 25.7 (6.7–79.2)	28.6 ± 9.5 30.8 (12.1–43.3)	15.6 ± 6.0+ 16.7 (2.3–27.1)	11.4 ± 6.8+ 11.6 (3.1–23.9)	10.8 ± 8.8++ 8.7 (0.6–29.6)
Parapneumonic effusion (II)	29	2.87 ± 3.32 1.5 (0.2–13.0)	6.6 ± 3.4 6.0 (1.0–16.3)	39.3 ± 14.3 37.7 (18.6–73.8)	4326 ± 17338 482 (123–94150)	18.0 ± 16.3 12.8 (1.2–60.3)	25.8 ± 12.2 25.8 (7.9–56.2)	18.8 ± 8.1 17.0 (6.6–40.6)	15.2 ± 8.1 15.5 (1.4–28.1)	21.9 ± 19.1 19.8 (1.3–67.6)
Malignant effusion (III)	41	7.14 ± 22.06** 1.0 (0.1–101)	5.5 ± 2.6* 5.7 (0.7–13.5)	42.4 ± 9.6** 42.1 (22.0–74.6)	1361 ± 2502** 776 (210–14796)	11.7 ± 7.4** 10.6 (2.3–29.4)	23.6 ± 10.6 21.2 (5.9–47.6)	19.0 ± 8.3** 16.5 (5.4–43.2)	19.2 ± 8.3** 21.2 (2.0–31.3)	26.6 ± 17.1** 24.8 (1.8–66.2)
p-value[b]		NS	< 0.003	< 0.0001	< 0.001	< 0.0001	NS	NS	< 0.0006	< 0.006

Data are expressed as mean ± standard deviation and median with range in parenthesis.

[a] Serum lactate dehydrogenase and its isoenzyme pattern of the healthy control subjects.

[b] *Kruskal-Wallis* ANOVA test; p value < 0.005 statistically significant (*Bonferroni*'s correction).

* p = 0.01 *Mann-Whithey* versus group II

** p < 0.005 *Mann-Whitney* versus group II

\+ p < 0.001 *Mann-Whitney* versus group III

++ p < 0.001 *Mann-Whitney* versus group III

Tab. 2 Absolute values (U/l) of lactate dehydrogenase in serum, lactate dehydrogenase and its isoenzyme concentration in the pleural effusions obtained from the studied groups, as well as the normal serum value of healthy control group (n = 48).

	n	Serum	Pleural effusions					
		LDH (U/l)	LDH (U/l)	LDH1 (U/l)	LDH2 (U/l)	LDH3 (U/l)	LDH4 (U/l)	LDH5 (U/l)
Controls	48	361 ± 54 362 (219–475)						
Transudative effusion (I)	23	485 ± 110 449 (298–665)	164 ± 41**++ 178 (43.0–233)	56 ± 33*++ 46.0 (12.9–109.3)	48 ± 21**++ 44.8 (14.8–82.2)	22 ± 13**++ 25.7 (2.8–52.8)	18 ± 12**++ 17.0 (5.7–46.6)	16 ± 16*++ 13.8 (1.1–53.0)
Parapneumonic effusion (II)	29	497 ± 356 380 (282–1857)	4326 ± 17338 482 (123–94150)	118 ± 212 71.4 (25.4–1130)	465 ± 1523 138 (37.5–8191)	660 ± 2487 16.9 (8.1–13275)	1154 ± 4973 63.2 (1.7–26456)	1991 ± 8480 70.3 (3.3–45097)
Malignant effusion (III)	41	564 ± 78 422 (236–2886)	1361 ± 2502** 776 (210–14796)	137 ± 305 67.9 (30.3–1775)	278 ± 495 161 (57.1–2885)	293 ± 653 130 (29.3–3728)	320 ± 609 175 (17.3–3388)	403 ± 605 192 (7.5–3018)
p-value[a]		NS	< 0.0001	0.05	< 0.0001	< 0.0001	< 0.0001	<0.0001

Data are expressed as mean ± standard deviation and median with range in parenthesis.

[a] *Kruskal-Wallis* ANOVA test; p value < 0.005 statistically significant (*Bonferroni*'s correction).

* p < 0.005 *Mann-Whitney* versus group II

** p < 0.001 *Mann-Whitney* versus group II

\+ p < 0.005 *Mann-Whitney* versus group III

++ p < 0.002 *Mann-Whitney* versus group III

Tab. 3 Logistic regression analysis for discriminating between group I (transudative effusion; n = 22) and groups II (parapneumonic effusion) + III (malignant effusion) combined (n = 61). Results expressed as log odds ratios of groups II (parapneumonic effusion) + III (malignant effusion) versus group I (transudative effusion) per unit increase of the explanatory variables (10 missing values); likelihood ratio tests used.

Explanatory variable (unit)	log odds ratio	Likelihood ratio test p-value
Lactate dehydrogenase (U/l)	0.0198	0.000
Glucose (mmol/l)	0.3716	0.0665
Protein (g/l)	0.1675	0.0194
(constant:	−11.8354)	

to be mentioned that the results given in tables 4 and 6 (and also in figs. 1 and 2) are slightly too optimistic. This is because the goodness-of-fit of a model to observations from which the model has been estimated is better than to new observations. Table 7 gives the predicted probabilities of belonging to group III rather than to group II per quartile of an explanatory variable, while adjusting for the other explanatory variables in the logistic regression model by putting them on their mean value. These predicted probabilities are calculated from the logistic regression model of table 5, fitted in the group of 58 patients belonging to either group II or group III, with non-missing values for the four variables involved. For not too high values of lactate dehydrogenase and high values of LDH2 and LDH4 (implying that the other lactate dehydrogenase isoenzyme activities are low) the probability of group III becomes higher than that of group II. Also a low glucose concentration increases the probability of group III.

Discussion

This study showed that, in agreement with others, including lactate dehydrogenase, glucose and protein as independent variables in the logistic regression yielded a strong discrimination between pleural effusions of transudative and exudative origin. Although total lactate dehydrogenase concentration is one of the properties used to discriminate between transudative and exudative effusions, this has no consequences for the present experimental setup, where the value of the lactate dehydrogenase isoenzymes is examined. The lactate dehydrogenase isoenzyme patterns were significantly different between transudative and exudative pleural effusions. In transudative effusions the lactate dehydrogenase isoenzyme pattern was similar to that of normal sera. Moreover, in exudative effusions the percentage of LDH1, LDH4, as well as LDH5 differed between parapneumonic effusions and malignant effusions. In contrast, with regard to the absolute lactate dehydrogenase (U/l) values no differences between both identified exudative effusions (group II and III) were demonstrated. Furthermore, statistical analysis indicated that the lactate dehydrogenase isoenzymes have no additional value in distinguishing between exudative effusions of malignant and non-malignant origin.

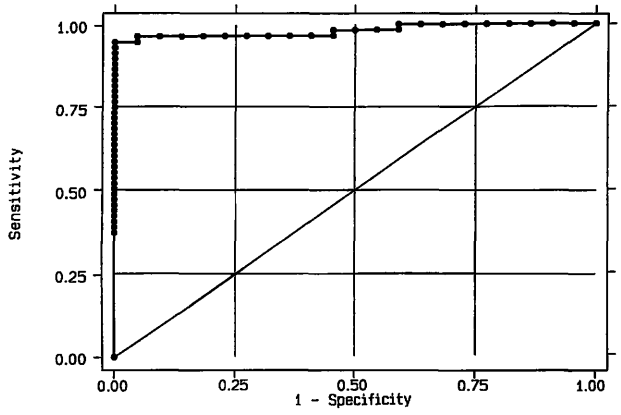

Fig. 1 Receiver-operating characteristic curve of the linear predictor score given by table 3: transudative effusion (group I) versus exudative effusion (group II + III). The total lactate dehydrogenase activity; the glucose together with the protein concentration were used in a linear combination (tab. 3), no other variables were necessary. Sensitivity is the probability of correctly predicting group II + III (probability (predicted II+III/observed II+III)). Specificity is the probability of correctly predicting group I (probability (predicted I/observed I)). Area under the receiver-operating characteristic curve is 0.9821.

Tab. 4 Observed versus predicted group membership following from the estimated logistic regression model in table 3.

	Predicted group membership (n)		
	Transudative effusion (I)	Parapneumonic effusion (II) + Malignant effusion (III)	Total
Observed			
Transudative effusion (I)	20	2	22
Parapneumonic effusion (II) + Malignant effusion (III)	2	59	61
Total	22	61	83

Sensitivity = portion of predicted parapneumonic effusion + malignant effusion among observed parapneumonic effusion + malignant effusion = 100 (59/61) = 96.7%

Specificity = portion of predicted transudative effusion among observed transudative effusion = 100 (20/22) = 90.9%

Reviewing the literature conflicting data were found. Until now, the only situation in which the isoenzyme analysis of pleural fluid has proven its value is when lactate dehydrogenase is in the exudative range and protein in transudative range. Only the relative values of lactate dehydrogenase isoenzymes, as percentage of the total lactate dehydrogenase were studied. The present study evaluated the absolute lactate dehydrogenase isoenzyme activity in the different pleural effusions as well. In agreement with *Richterich & Burger* (20), the lactate dehydrogenase isoenzyme pattern of the benign effusions, i. e. transudative effusions, reflected the serum pattern. In contrast, *Fröhlich & Keller* (21) reported that benign effusions were characterized by maximal activity of LDH4 and LDH5. This was in line with the results of a study by *Light & Ball* (9). These authors reported that transudative pleural efflusions – having a total lactate dehydrogenase lower than 200 U/l or 60% of the serum value – had a slightly higher percentage of LDH4 and LDH5 compared to the serum values. Our results showed that mainly the percentages of LDH4 and LDH5 are helpful in discriminating malignant effusions from benign exudative effusions, i. e. parapneumonic effusions. Others showed that malignant effusions were characterized by increased activity of LDH2, whereas *Richterich & Burger* (20), as well as *Fröhlich & Keller* (9, 21) also reported an increase of the percentages of LDH3 and LDH4.

Vergnon et al. (17) found an increase of the LDH5 isoenzyme activity to be a good marker of malignant pleural effusion, except when the pleura is involved by malignant lymphoma or small cell lung carcinoma. Moreover, they suggested that the LDH5 isoenzyme activity in pleural fluid appears to be an accurate marker in the follow-up of malignant pleural effusions.

Tab. 5 Logistic regression analysis for discriminating between parapneumonic effusion (group II, n = 27) and malignant effusion (group III, n = 31). Results are expressed as log odds ratios of group III versus group II per unit increase of the explanatory variable (12 missing values); likelihood ratio tests used.

Explanatory variable (unit)	log odds ratio	Likelihood ratio test p-value
Lactate dehydrogenase (U/l)	−0.0030	0.0234
Glucose (mmol/l)	−0.1750	0.0645
LDH2 (U/l)	0.0051	0.0252
LDH4 (U/l)	0.0088	0.0356
(constant:	1.4495)	

Tab. 6 Observed predicted group membership following from the estimated logistic regression model in table 5.

	Predicted group membership (n)		
	Parapneumonic effusion (II)	Malignant effusion (III)	Total
Observed group membership			
Parapneumonic effusion (II)	14	13	27
Malignant effusion (III)	7	24	31
Total	21	37	58

Sensitivity = portion of predicted malignant effusion among observed malignant effusion = 100 (24/31) = 77.4%
Specificity = portion of predicted parapneumonic effusion among observed parapneumonic effusion = 100 (14/27) = 51.9%

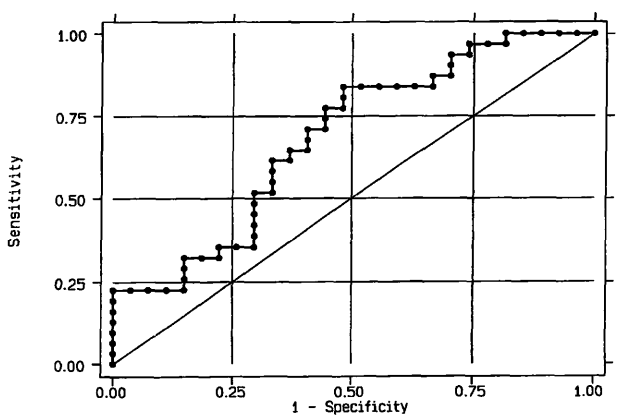

Fig. 2 Receiver-operating characteristic curve of the linear predictor score given by table 5: exudative effusions group II (parapneumonic) versus group III (malignant). The total lactate dehydrogenase (LDH) activity, glucose, absolute value of the LDH2 and LDH4 concentration were combined in a linear predictor score (tab. 5). Sensitivity is the probability of correctly predicting group III (probability (predicted III/observed III)). Specificity is the probability of correctly predicting group II (probability (predicted II/observed II)). Area under the receiver-operating characteristic curve is 0.6834.

Tab. 7 Predicted probability of malignant effusion (group III) versus parapneumonic effusion (group II) in quartiles of an explanatory variable, adjusted for the other explanatory variables in the logistic regression model.

Variable	Quartile	Predicted probability of malignant effusions (III)
Lactate dehydrogenase	1. < 327	1.00
	1. 327–776	1.00
	3. 776–1377	1.00
	4. > 1377	0.57
Glucose	1. < 3.7	0.66
	2. 3.70–5.75	0.55
	3. 5.75–7.3	0.50
	4. > 7.30	0.33
LDH2	1. < 98.6	0.17
	2. 98.6–157.5	0.22
	3. 157.5–271.9	0.29
	4. > 271.9	0.65
LDH4	1. < 35.6	0.00
	2. 35.6–123.5	0.00
	3. 123.5–305.8	0.01
	4. > 305.8	0.45
Mean		0.51

In the present study significant differences in the lactate dehydrogenase ratio pleural fluid to serum were found only between the transudative effusions (group I) and exudative effusions (group II and III, respectively). Moreover, the isoenzyme pattern in transudative effusions is similar to the serum isoenzyme pattern. In line with this, *Dev* et al. (16) found a significant difference in total lactate dehydrogenase, lactate dehydrogenase ratio pleural fluid to serum and lactate dehydrogenase isoenzymes. The value was intermediate in malignancy and other exudative conditions. The LDH5 activity ratio pleural fluid to serum tended to be higher in pleural effusions of mesotheliomal origin than in those from non-mesothelial tumours. No relationship was found between the histologic pattern of the malignancy and the pleural fluid isoenzyme pattern.

Conclusions

Pleural fluid lactate dehydrogenase concentration, together with glucose and protein levels had a strong discriminatory power in the initial classification of pleural effusions into transudate and exudate. From our data it became clear that lactate dehydrogenase isoenzymes have no additional discriminative value, neither for discriminating between transudative and exudative effusions, nor for the discrimination between parapneumonic and malignant effusions or pleuritis carcinomatosa.

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