SHORT REPORT

New criteria for the differentiation between transudates and exudates

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J Clin Pathol 2002;**55**:69–71

Aims: To investigate whether cholesterol and lactate dehydrogenase (LDH) measurements in fluids are more sensitive and specific markers for differentiating between exudates and transudates, as confirmed clinically, than the measurement of fluid total protein concentrations alone.
Patients/Methods: Serum, pleural fluid, and ascitic fluid from 61 unselected patients were analysed retrospectively for LDH, cholesterol, and total protein. Clinical classification of transudate or exudate was reached independently by reviewing clinical details and laboratory data.
Results: Of 54 samples (40 pleural fluid and 14 ascitic fluid), 30 were classified clinically as exudates and 24 as transudates. Fluid LDH and fluid to serum protein ratio measurements were equally good at differentiating between exudates and transudates, with a sensitivity of 90%, a specificity of 79%, a positive predictive value (PPV) of 84%, and a negative predictive value (NPV) of 86%. A combination of these parameters improved sensitivity to 100% and NPV to 100%, but lowered the specificity to 71% and PPV to 81%. This combination achieved a higher efficiency than Light's criteria.
Conclusion: Routine measurement of fluid LDH values and the calculation of fluid to serum total protein ratios will aid in differentiating exudates from transudates.

It is clinically important to classify pleural and ascitic fluids into exudates and transudates because this is indicative of the underlying pathophysiological process involved. Such a distinction allows appropriate investigations to be instigated, enabling better patient management. Light *et al* used a fluid to serum total protein ratio > 0.5, a fluid lactate dehydrogenase (LDH) value > 200 U/litre, or a fluid to serum LDH ratio > 0.6 to diagnose exudates, with the remaining fluids being transudates.[1] This has been reported as the best method for discriminating between exudates and transudates,[2] although other workers[3] have modified the cut off points used by Light *et al*.[1] A recent meta-analysis of studies on pleural fluids[4] found that no one test was clearly superior in differentiating exudates from transudates. Although paired and triple tests had higher diagnostic accuracies than individual tests, no clearly superior test combination was identified. However, many patients with cardiac failure have fluid total protein concentrations in the exudative range, and high total protein values in ascitic fluid are also seen in some cases of chronic liver disease.[5]

One study showed that the measurement of cholesterol in the fluid had a higher diagnostic accuracy,[6] although others have not confirmed this.[7] Serum cholesterol exists in large lipoprotein complexes and increased vascular permeability allows serum cholesterol to pass into either the pleural or peritoneal cavity. A similar mechanism exists for the movement of LDH. However, LDH is also released by neutrophils and so may be important in infections.

There is no ideal biochemical marker that allows complete discrimination between transudates and exudates. Light's criteria have high sensitivity but lower specificity and therefore do not have a high diagnostic efficiency.[8] In a general hospital, a high proportion of the fluids are transudates and this combination would not be efficient. The purpose of our study was to identify an optimum marker combination to differentiate between exudates and transudates by the measurement of cholesterol and LDH in fluids, in addition to the usual measurement of fluid total protein.

METHODS

Our study was retrospective, conducted on 61 unselected samples of pleural and ascitic fluid collected at a district general hospital between 1994 and 1996. The study was approved by the St Helier research and ethics committee.

Pleural and ascitic fluid, together with serum collected at the same time, were analysed using standard laboratory methods for total protein (biuret), cholesterol (cholesterol oxidase), and LDH (using a kinetic UV lactate to pyruvate method with the serum upper normal limit being < 215 U/litre (Axon, Technicon; Bayer Ltd, Newbury, UK). The clinical classification of transudate or exudate was reached independently by a retrospective review of the course of the illness through examination of the patient notes and other laboratory data, which included the fluid total protein, but not fluid LDH or fluid cholesterol. Only one reviewer was used for most of the cases and this reviewer was not involved in the care of the patients or in the analysis of the fluid. When there was any uncertainty about the clinical diagnosis, a senior colleague was consulted who came to a conclusion independently. Samples were only included in our study if there was certainty about the clinical diagnosis and if there was agreement between the two observers in those less clear cut cases. All samples were sent for cytology, microbiological microscopy, and culture. For suspected malignancy with negative cytology, pleural biopsies were taken and, if negative, thoracotomy or thoracoscopy was performed. Bronchoscopy was done if indicated. Where clinically relevant, full blood count; standard renal, liver, bone, and thyroid profiles; chest *x* rays; computed tomography scan; echocardiogram; liver ultrasound; and biopsies were done. The clinical classifications were arrived at using strict predetermined clinical criteria. Congestive cardiac failure (CCF) was classified when there was evidence of an enlarged heart on chest *x* ray or echocardiogram, signs of pulmonary oedema or peripheral oedema, and response to treatment for CCF. Renal failure was determined to be the underlying cause where the patient had raised urea (> 20 mmol/litre) and creatinine (> 167 mmol/litre), signs of fluid

Abbreviations: CCF, congestive cardiac failure; LDH, lactate dehydrogenase; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic

Table 1 Statistical analysis of the parameters used to classify transudates and exudates, expressed as percentage (95% confidence intervals)

	Fluid total protein	Fluid cholesterol	Fluid LDH	Fluid:serum total protein	Fluid LDH + fluid:serum total protein	Light's criteria
Cut off	28 g/l	0.8 mmol/l	130 U/l	0.4		
Sensitivity	83 (69 to 96)	87 (69 to 96)	90 (73 to 98)	90 (73 to 98)	100 (91 to 100)	90 (73 to 98)
Specificity	75 (53 to 90)	67 (45 to 84)	79 (58 to 93)	79 (58 to 93)	71 (51 to 80)	67 (45 to 84)
Efficiency	80 (66 to 89)	78 (64 to 88)	85 (73 to 93)	85 (73 to 93)	87 (78 to 92)	80 (66 to 89)
PPV	81 (63 to 93)	76 (59 to 89)	84 (67 to 95)	84 (67 to 95)	81 (66 to 89)	77 (60 to 90)
NPV	78 (56 to 93)	80 (56 to 94)	86 (65 to 97)	86 (65 to 97)	100 (87 to 100)	84 (61 to 96)
Youden's index	0.58	0.53	0.69	0.69	0.71	0.57

Cut off values were obtained from ROC analysis. Sensitivity is TP/(TP+FN), specificity is TN/(TN+FP), efficiency is (TP+TN)/(TP+TN+FP+FN), where TP is the number of true positive diagnoses (number of exudates correctly diagnosed), TN is the number of true negative diagnoses (number of transudates correctly diagnosed), FP is the number of false positive diagnoses (number of transudates undiagnosed), and FN is the number of false negative diagnoses (the number of exudates undiagnosed). Youden's index can be used to compare the false negative and false positive rates of different tests. For fluid LDH, the probability of a false negative, Pr(FN) is 3/30 and the probability of a false positive, Pr(FP) is 5/24. Youden's index = 1–(3/30+5/24)=0.69. The higher the value, the lower the false negative and false positive rates.
LDH, lactate dehydrogenase; ROC, receiver operator characteristic.

Table 2 Fluids classified into exudates and transudates using clinical diagnosis and by analysis of fluid and serum total protein, lactate dehydrogenase (LDH), and cholesterol

Clinical diagnosis	N	Fluid total protein		Fluid cholesterol		Fluid LDH		Fluid: serum total protein		Fluid LDH + fluid:serum total protein		Light's criteria	
		TP	FN	TP	FN	TP	FN	TP	FN	TP	FN	TP	FN
Exudates total	30	25	5	26	4	27	3	27	3	30	0	27	3
Malignancy	22	19	3	19	3	20	2	20	2	22	0	19	3
Infection	5	3	2	4	1	4	1	4	1	5	0	5	0
Other*	3	3	0	3	0	3	0	3	0	3	0	3	0
		TN	FP	TN	FP	TN	FP	TN	FP	TN	FP	TN	FP
Transudates total†	24	18	6	16	8	19	5	19	5	17	7	16	8
CCF	13	7	6	7	6	10	3	9	4	11	2	8	5
Cirrhosis	6	6	0	6	0	6	0	6	0	6	0	5	1
Renal failure	4	2	2	2	2	3	1	4	0	4	0	3	1
Hypoalbuminaemia	4	4	0	3	1	2	2	3	1	3	1	2	2

*One case of systemic lupus erythematosus, one case of pelvic abscess, and one case of reactive pleural thickening; †includes two patients with both CCF and chronic renal failure and one with both CCF and hypoalbuminaemia.
CCF, congestive cardiac failure; FN, false negative; FP, false positive; TN, true negative; TP, true positive.

overload, and in some cases, evidence of renovascular disease or evidence from renal biopsy. Some of these patients were on peritoneal dialysis or haemodialysis. Liver cirrhosis was diagnosed on the basis of a known history of increased alcohol consumption with evidence of cirrhosis on liver biopsy or other signs of chronic liver disease. Malignant exudates were diagnosed on the basis of positive cytology or histology. An infective exudate was diagnosed when there was clear evidence of an infection with positive cultures or empyema and a clear response to antibiotic treatment.

The statistical analysis was performed using Microsoft Excel and Astute (DDU Software, Leeds, UK). Results were evaluated by receiver operating characteristic (ROC) analysis. ROC curves were generated for each of the individual tests and the cut off points determined to the highest level of accuracy and precision. The sensitivities and specificities were determined from the ROC curves. The 95% confidence intervals, positive and negative predictive values, and Youden's index (table 1) were calculated using standard methods.

RESULTS

Of the 61 cases, it was not possible to come to a clinical diagnosis in seven, because of a lack of data, conflicting results, or coexisting disease processes. Of the remaining 54 samples, 40 were pleural fluids and 14 were ascitic fluids. The samples were from 34 men and 20 women. The average age of the patients was 70 years (range, 20–96). The patients represented the usual range of clinical conditions encountered in a district general hospital.

Table 2 shows the fluids classified into exudates or transudates using clinical criteria and biochemical analysis of fluid total protein, fluid cholesterol, fluid LDH, fluid to serum total protein ratio, and Light's criteria. Pleural and ascitic fluid cut off values did not differ. The usefulness of each of the parameters for identifying exudates was evaluated in terms of sensitivity, specificity, and efficiency (table 1).

Fluid LDH measurements and fluid to serum protein ratio measurements were equally good at differentiating between exudates and transudates. Fluid LDH misclassified eight of the 54, consisting of three exudates (two malignancies and one abscess) and five transudates, with a sensitivity of 90%, a specificity of 79%, a positive predictive value (PPV) of 84%, and a negative predictive value (NPV) of 86%. Fluid LDH measurements correctly classified more cases of transudates as a result of CCF than did fluid total protein, fluid cholesterol, or fluid to serum total protein ratio measurements, which misclassified many of those cases as exudates, as did Light's criteria. Fluid LDH measurements also correctly classified more infections (pneumonia) as exudates than did fluid total protein measurements. Although the numbers of cases in these subanalyses were small, the correlation appeared to be good. Fluid total protein measurements were not as good at differentiating between exudates and transudates as the measurement of fluid LDH values, misclassifiying 11 of the 54 cases (three malignancies, two infections, and six cases of CCF). However, when fluid to serum total protein ratios were used, the sensitivity was improved from 83% to 90% and the specificity from 75% to 79%, and the results were comparable to the measurement of fluid LDH.

Take home messages

- The combination of fluid lactate dehydrogenase measurements and fluid to serum total protein ratios is useful in differentiating exudates from transudates
- Using this combination could help in patient management and avoid unnecessary testing

Calculating the fluid serum total protein ratio improved the classification of exudates caused by malignancy and infection and also the classification of transudates as a result of CCF and renal failure. When both fluid LDH and the fluid to serum total protein ratio were used in combination, such that an exudate was classified if either of these parameters was found to be positive, then all of the exudates were correctly classified. Therefore, in combination, these two measurements together enabled an accurate way to identify true exudates, with a sensitivity of 100%, a specificity of 71%, a PPV of 81%, and an NPV of 100%. Table 1 shows that the 95% confidence intervals were wide for the individual tests, resulting in overlap between values for the different tests, and that the intervals were less when the two parameters were used. The measurement of fluid cholesterol conferred no advantage over measuring fluid total protein, fluid to serum total protein ratio, or fluid LDH values, although fluid cholesterol measurements were better than fluid total protein at correctly classifying cases of pneumonia as exudates.

DISCUSSION

There is no biochemical marker that allows a complete differentiation between transudates and exudates.[1–9] In most hospitals, only fluid total protein is measured routinely to classify the fluid as a transudate or an exudate. The measurement of fluid LDH and the fluid to serum protein ratio in ascitic and pleural fluid substantially improves the diagnostic classification of these fluids as transudates or exudates, thus aiding clinical diagnosis. The measurement of fluid LDH was found to be especially helpful in those cases of CCF when fluid total protein values are borderline and often misleading. In such cases, the patient (who is often elderly), undergoes several unnecessary and expensive investigations in the search for a cause of the exudate, rather than being treated appropriately for CCF. Fluid LDH measurements were also better at classifying infective causes of an exudate compared with fluid total protein measurements alone. Calculating the fluid to serum total protein ratio also improves the sensitivity and specificity, especially in cases of malignancy, infection, and renal failure. When both of these parameters were used together, such that if either was positive, the fluid was classified as an exudate, this resulted in an improved diagnosis of exudates, but at the cost of increased misclassification. Therefore, we suggest that the routine measurement of fluid LDH and the calculation of the fluid to serum total protein ratio would aid diagnosis.

We have shown that the biological markers used to discriminate transudates and exudates are not always in agreement. Light *et al* had a predominance of exudates (103 of 150 cases) and a classification used to diagnose exudates.[1] The misclassification rate was reduced to 5–12% using a combination of two parameters, and to 3% with a combination of three parameters. The combination of parameters leads to an improved classification of exudates. Many of the studies had an exudate to transudate ratio of 3 : 1 which leads to improved sensitivity over specificity.[8 9]

In our study, if both the fluid LDH is > 130 U/litre or the fluid to serum total protein ratio is > 0.4, the fluid should be regarded as an exudate. The cost of measuring LDH fluid and calculating the fluid to serum total protein ratio in all cases will be negligible but helpful to the clinician in determining what further tests need to be done, thus decreasing the number of unnecessary aspirations, computed tomography scans, and bronchoscopies carried out in looking for possible malignancy.

ACKNOWLEDGEMENTS

We thank Dr N Cooke for his support throughout the study; Mrs E Limb for help with statistical analysis; Mrs B Rough for help with data and analysis, Mr P Makwana for assistance with the biochemical analysis; and Mrs R Wilkinson and Mrs S Matthews for their secretarial skills.

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Accepted for publication 18 July 2001

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