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Research article

Diagnostic Utility of Pleural Effusion and Serum Cholesterol, Lactic Dehydrogenase and Protein Ratios in the Differentiation between Transudates and Exudates

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Abstract: This is a descriptive study carried out in Khartoum state hospitals during the period from May 2012 to April 2014. The study aimed to evaluate the diagnostic role of the pleural effusion/serum (CHOL, LDH, and protein) ratios in the differentiation between exudate and transudate pleural effusion. As a part of the investigation, 135 serum and pleural effusion samples were collected from patients with accumulated plural effusion. Prior to testing, 5 mL of venous blood and 20 mL of pleural effusion samples were prepared in accordance with specific testing requirements. Exudative pleural effusions were observed in 95 (70.4%) samples, of which 64 (67.4%) belonged to male patients and 31 (32.6%) to females. The calculated means for CHOL, LDH, and protein levels in pleural effusion and serum samples between exudate and transudate effusion showed statistically significant differences with the *p*-value = 0.000. In distinguishing between exudative and transudate pleural effusion, a high Pearson correlation was observed between CHOL ratio and clinical diagnosis (r = 0.971), as well as between CHOL level in effusion samples and LDH level in serum samples (r = 0.867). Sensitivity, specificity, positive predictive value, and negative predictive value analysis of the parameters in the differentiation between exudate and transudate samples revealed the following values: 97.7% and 100%, 100%, and 95%, respectively, for the CHOL ratio; 86%, 97.4%, 97.4%, and 97%, respectively, for the LDH ratio; and 81.4%, 81.6%, 89.7%, and 70.4%, respectively, for the protein ratio. On the basis of the study findings, it could be concluded that estimation of CHO, LDH, and protein ratios can assist in the differentiation between exudative and transudate pleural effusion and thus patient management. Hence, this approach should be included in routine laboratory analyses of pleural effusions. Nevertheless, additional techniques should be incorporated in the diagnosis of doubtful pleural effusions, as this will improve the diagnostic sensitivity and specificity in this setting.

Keywords: pleural effusion; transudates; exudates; cholesterol; protein; lactic dehydrogenase

1. Introduction

Accumulation of fluids in the pleural cavity is classified into transudates and exudates. Transudate is usually composed of ultra filtrates of plasma and poor cellular content and protein concentration. On the other hand, in typical exudates, the cellular content is much greater than that of transudates and a greater variety of cells is usually present. These cells may be inflammatory or neoplastic, depending on the cause of the exudate. The concentration of protein is often greater than that found in transudate, i.e. > 3 g/dL, but not invariably so, as there is considerable overlap between the ranges [1,2]. The traditional classification of pleural effusion into transudates and exudates is still useful because it indicates the physiopathologic mechanism involved. More specifically, pleural exudates emerge due to alteration of hydrostatic and/or colloid osmotic pressures in plural capillaries, or as a result of fluid passing from the peritoneal cavity to the pleural cavity via a defect in the diaphragm or lymph vessels. The criteria proposed by Light et al. in 1972 are currently used to discriminate between transudates and exudates [3]. However, the distinction between transudates and exudates is not presently clear due to a possible overlap between the two. To date, different parameters have been applied to differentiate between the two conditions, such as pleural fluid protein level, pleural fluid cholesterol (CHOL), lactic dehydrogenase (LDH) level, and pleural fluid/serum protein ratio [4,5]. These approaches are unreliable, as they tend to result in misclassification of many effusions [6]. This study aimed to determine the diagnostic utility of CHOL, LDH, and protein ratios in the differentiation between transudate and exudate in pleuritis cases of different etiology and assess the relationship between pleural effusion and serum level of CHO, LDH, and protein.

2. Materials and Methods

2.1. Study design

This is a descriptive study aiming to evaluate the diagnostic role of the pleural effusion/serum (CHOL, LDH, and protein) ratios in the differentiation between exudate and transudate effusion. The study was conducted in Khartoum state hospitals, Sudan, during the period from May 2012 to May 2014.

2.2. Study population

Pleural effusion and serum samples were collected from 135 patients with definite diagnosis of having pleural effusion, all of whom were aged 18 years or older. All patients gave informed consent for participating in the study. The following evidence was used to include or exclude the cases [7].

1) Congestive heart failure: presence of clinical features (increased JVP, tachycardia, ventricular gallop) with cardiomegaly or echocardiac evidence of cardiac dysfunction.
2) Renal diseases: elevated urea (> 20 mmol/L) or creatinine > 167 μmol/L with or without signs or symptoms of fluid overload.
3) Malignancy: confirmed by cytology or histological proof of malignant tumor and in absence of all other conditions associated with pleural effusion.

4) Liver cirrhosis: positive ultrasonography or CT findings with clinical and lab evidence of hepatic derangements and portal hypertension.
5) Infective effusion: clear evidence of infection (positive microbiologic culture), elevated CRP or leukocytosis or positive sputum stain.
6) Hypoalbuminemia: serum albumin < 20 mg/L.

2.3. Sample collection and processing

Pleural effusion and serum samples were collected from all patients. Thoracentesis was performed to collect pleural effusion, while serum was collected from the venous blood using a 5 mL syringe. CHOL, LDH, and protein levels were measured in both samples.

The CHOL level was measured using an enzymatic colorimetric method, whereby all cholesterol is freed from the lipoproteins and is subsequently oxidized. When the oxidized CHOL is formed, H_2O_2 is produced, which in turn reacts with the reagent 4-aminoantipyrine to form a red compound. The increase in absorbance at the 520 nm wavelength is proportional to the CHOL level (Cobas Integra system; Roche Diagnostic). LDH level was measured by UV spectrophotometry at 36 oC and 340 nm. In this process, LDH catalyses the oxidation of lactate to pyruvate in the presence of Nicotinamide Adenine Dinucleotide (NAD), which is subsequently reduced to NADH. The rate of NADH formation measured at 340 nm is directly proportional to the serum LDH activity (TECO DIAGNOSTICS). Protein level was measured by quantitative calorimetric (Burt) method, whereby protein forms a colored chelate complex with cupric ions (Cu^{2+}) in an alkaline environment containing sodium potassium tartrate. The product yields a light blue to violet complex that absorbs light at 540 nm. One cupric ion forms a colored coordination complex with four to six peptide bonds in its vicinity. The intensity of the color produced is proportional to the amount of peptide bonds participating in the reaction (HiPer® Protein Estimation Teaching Kit (Quantitative) HimediaLaboratories TM).

2.4. Statistical analysis

The data collected as a part of the study was analyzed by using Statistical Package for Social Sciences (*SPSS*). Descriptive and other statistics test results were expressed in tables and figures.

3. Results

In this study, the diagnostic utility of CHOL, LDH, and protein ratios in the differentiation between exudate and transudate pleural effusions was assessed. The study sample comprised of 135 patients aged > 20 (mean age 51), referred to different hospitals in the Khartoum State, in whom pleural effusion was clinically diagnosed. As shown in Table 1 and Figure 1, two groups of individuals were classified according to the diagnostic yields of their effusions. In 95 (70.4%) of study participants, exudative effusion was diagnosed, whereas the remaining 40 (29.6%) had transudate effusion.

Table 2 and Figure 2 show the distribution of the study population by effusion type and gender. As can be seen, both exudative and transudate effusion was more predominant in male patients, at 64 (67.4%) and 23 (56.5%), respectively.

Table 1. Distribution of the study population by effusion type.

Eff. type	Frequency	Percent (%)
Exudate	95	70.4%
Transudate	40	29.6%
Total	135	100.0%

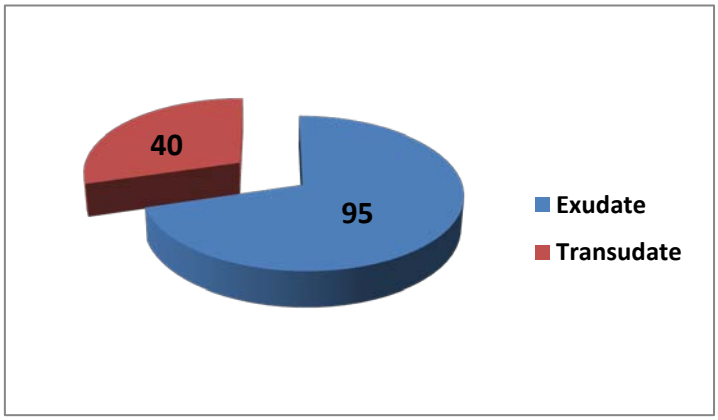

Figure 1. Distribution of the study population by effusion type.

Table 2. Distribution of the study population by effusion type and gender.

	Male		Female		Total	
Eff. Type	No	%	No	%	No	%
Exudate	64	67.4%	31	32.6%	95	70.4%
Transudate	23	56.5%	17	42.5%	40	29.6%
Total	87	64.4	48	45.6	135	100.0%

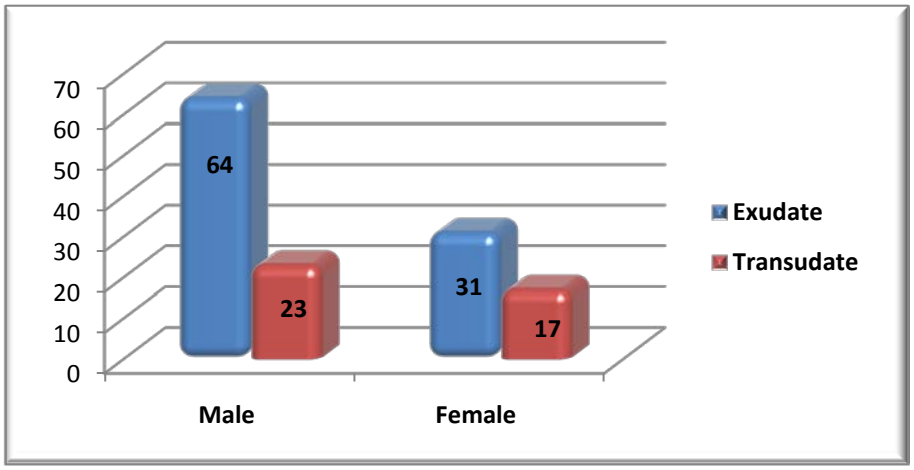

Figure 2. Distribution of the study population by effusion type and gender.

The distribution of the study population by effusion type and age is shown in Table 3 and Figure 3. In patients with exudative effusion, the majority (48, or 50.5%) of the study population were in the

> 60 age group, followed by the 41–60, and 20–40 age groups, which comprised of 28 (29.5%) and 19 (20%) individuals, respectively. On the other hand, transudate effusion was the most prevalent in the 41–60 age group (18 or 45%), followed by the > 60, and 20–40 age groups, which consisted of 12 (30%) and 10 (25%) patients, respectively.

Table 3. Distribution of the study population by effusion type and age.

	20–40		41–60		> 60		Total	
Eff. type	No	%	No	%	No	%	No	%
Exudate	19	20 %	28	29.5 %	48	50.5 %	95	70.4 %
Transudate	10	25 %	18	45 %	12	30 %	40	29.6 %
Total	29	21.5 %	46	34 %	60	44.4 %	135	100 %

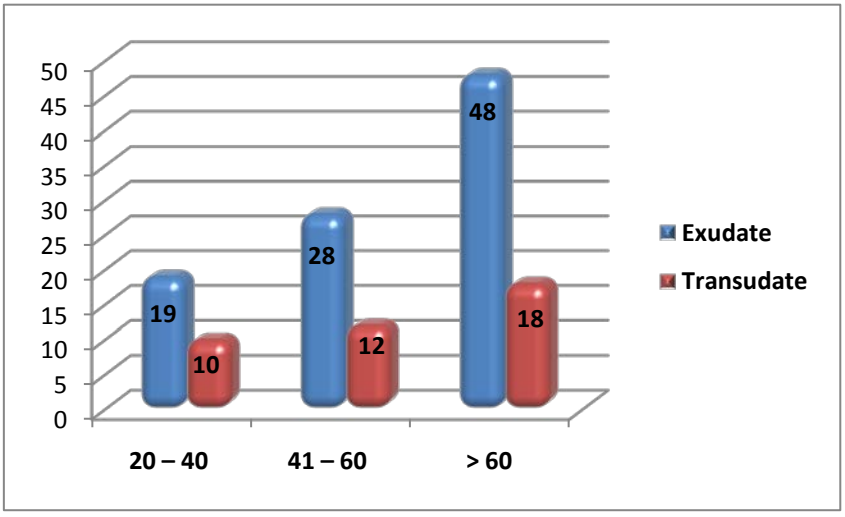

Figure 3. Distribution of the study population by effusion type and age.

Table 4 and Figure 4, presents the study population distribution by effusion type and clinical diagnosis. As can be seen from the data, among patients with exudative effusion, tuberculosis was the most common cause, diagnosed in 52 (54.7%) individuals, followed by pneumonia (18, 18.9%), pulmonary cancer (10, 10.5%), pulmonary embolism (9, 9.5%), and rheumatoid disease (6, 6.3). However, at 22 (55%), hepatic cirrhosis was the most prevalent condition among patients with transudate effusion, followed by congestive heart failure, which affected 18 (45%) individuals.

Table 4. Distribution of the study population by effusion type and clinical diagnosis.

	T.B		Pneu.		Pulm Ca.		Pulm emboli		Rheum Disease		Hepatic Cirrhosis		CHF		Total	
Eff.	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Exud	52	54.7%	18	18.9%	10	10.5%	9	9.5%	6	6.3%	0	0%	0	0%	95	70.4%
Trans	0	0	0	0%	0	0%	0	0%	0	0%	22	55%	18	45%	40	29.6%
Total	52	38.5%	18	13.3%	10	7.4%	9	6.7%	6	4.4%	22	16.3%	18	14.8%	135	100%

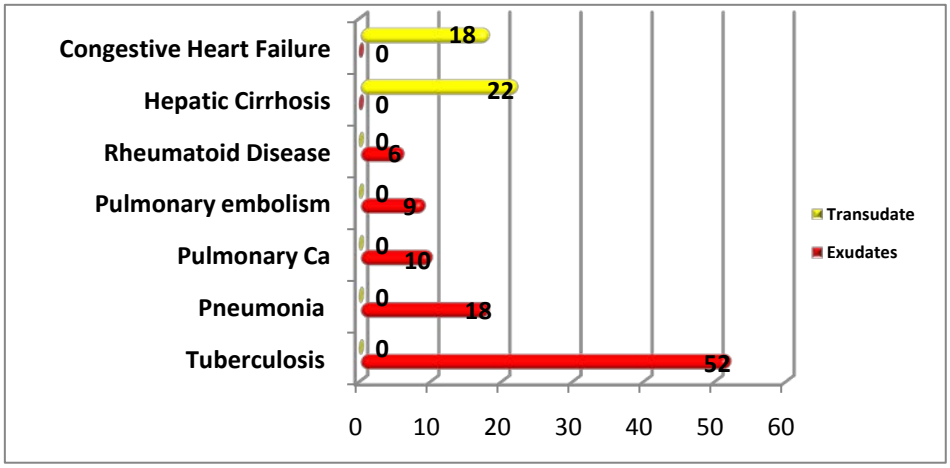

Figure 4. Distribution of the study population by effusion type clinical diagnosis.

Table 5 shows the levels of CHOL, LDH, and protein in serum and effusion samples among the study population. The level of all studied parameters in both serum and effusion fluid was significantly higher in the patients in the exudative group compared to those affected by transudate effusion. The differences among the mean values of all parameters was statistically significant at $p = 0.000$.

Table 5. CHOL, LDH, and protein levels in serum and effusion in the study population. (mean ± standard error of mean SEM) * *p*-value = 0.000.

Parameter	Type of sample	Type of effusion	Mean ± SEM
CHOL	Pleural fluid	Exudate	1.92 ± 0.75 mmol/L *
		Transudate	0.52 ± 0.28 mmol/L *
	Serum	Exudate	3.56 ± 0.84 mmol/L *
		Transudate	1.63 ± 0.75 mmol/L *
Protein	Pleural fluid	Exudate	3.56 ± 095 g/dL *
		Transudate	0.93 ± 0.35 g/dL *
	Serum	Exudate	5.25 ± 0.88 g/dL *
		Transudate	1.55 ± 0.61 g/dL *
LDH	Pleural fluid	Exudate	285 ± 25 IU *
		Transudate	160 ± 22 IU *
	Serum	Exudate	235 ± 45 IU *
		Transudate	134 ± 18 IU *

Pearson correlation between the CHOL, LDH, and protein levels in serum and effusion samples is shown in Table 6. As can be seen from the data, high correlation was observed between CHOL level in effusion samples and LDH level in serum samples with $r = 0.867$. Similarly, CHOL level in serum samples was correlated with LDH level in effusion samples, as was LDH level in serum samples and protein level in effusion samples (with $r = 0.855$ and $r = 0.824$, respectively). A relatively good association was observed between protein and CHOL levels in effusion samples, with $r = 0.791$. Similarly, Pearson correlation values indicated association between the CHOL, LDH, and protein ratios and clinical diagnosis. In particular, high correlation was observed between CHOL ratio and clinical

diagnosis, with $r = 0.971$), as well as LDH and protein ratios (at $r = 0.863$ and $r = 0.597$, respectively).

Table 6. Pearson correlation (*r*) of CHOL, LDH, and protein levels in serum and effusion samples.

Parameters	CHOL. Seru.		CHOL. Eff.		LDH Seru.		LDH Eff.		Prot. Seru.		Prot. Eff.	
	r	sig	*r*	sig	*r*	sig	*r*	sig	*r*	sig	*r*	sig
CHOL.Seru.	1		0.777**	0.000	0.673**	0.000	**0.855****	**0.000**	0.529**	0.000	0.532**	0.000
CHOL. Eff.	0.777**	0.000	1		**0.867****	**0.000**	0.667**	0.000	0.061	0.000	0.791**	0.000
LDH Seru.	0.673**	0.000	**0.867****	**0.000**	1		0.761**	0.000	0.207**	0.005	0.824**	0.000
LDH Eff.	**0.855****	**0.000**	0.667**	0.000	0.761**	0.000	1		0.690**	0.000	0.630**	0.000
Prot. Seru.	0.529**	0.000	0.061**	0.000	0.207**	0.005	0.690**	0.000	1		0.699**	0.000
Prot. Eff.	0.532**	0.000	0.791**	0.000	.824**	0.000	0.630**	0.000	0.699**	0.000	1	

** Correlation is significant at the 0.01 level (2-tailed).

Table 7 shows the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the CHOL, LDH, and protein ratios in differentiating between exudates and transudates. The highest values of these indicators pertained to the CHOL ratio, which showed 97.7% sensitivity, 100% specificity, 100% positive predictive value, and 95% negative predictive value. This was followed by the LDH ratio, with 86% sensitivity, 97.4% specificity, 97.4% positive predictive value, and 97% negative predictive value, and finally protein ratio, with 81.4% sensitivity, 81.6% specificity, 89.7% positive predictive value, and 70.4 % negative predictive value.

Table 7. Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) for CHOL, protein and LDH ratio.

Parameters	Sensitivity	Specificity	PPV	NPV	*p* value
CHOL ratio	97.7%	100.0%	100.0%	95.0%	< 0.0001
Protein ratio	81.4%	81.6%	89.7%	70.4%	< 0.0001
LDH ratio	86.0%	97.4%	97.4%	79.0%	< 0.0001

4. Discussion

This study assessed the diagnostic utility of CHOL, LDH, and protein ratios in differentiating between exudative and transudate pleural effusion of different etiologies. The study sample comprised of 135 patients with accumulated pleural effusion, of whom 93 (68.9%) were diagnosed with exudates and 42 (31.1%) with transudates. Subsequent analyses revealed that exudate effusion was more prevalent in males (64, 67.4%) and among patients aged > 60 years old (48, 50.5%). Tuberculosis was the most frequent cause of pleural effusion, with 52 (38.5%) cases, followed by hepatic cirrhosis (22, 16.3%), which is in line with the findings reported by Liam et al. [8], who suggested that the most common cause of exudative effusion was tuberculosis. The same results were also obtained by Kalaajieh [9], who concurred that tuberculosis is the most frequent cause of exudative pleural effusions.

Cholesterol CHOL ratio identified exudative effusion with a sensitivity of 97.7% and specificity

of 100%, whereas LDH ratio had a sensitivity of 86.0% and specificity of 97.4%. Finally, protein ratio achieved sensitivity and specificity of 81.4% and 81.6%, respectively. These results are consistent with those reported by Wilcox et al. [10], who concluded that Light's criteria, cholesterol and pleural fluid LDH levels, and the pleural fluid cholesterol-to-serum ratio are the most accurate diagnostic indicators for pleural exudates. Sánchez et al. [11] reported similar results and concluded that the cholesterol in pleural liquid/cholesterol in serum quotient was the most productive and useful parameter (with 96% sensitivity and 97% specificity).

Pearson correlation test of the CHOL, LDH and protein ratio yielded 0.971, 0.863, and 0.597 values, respectively. This result suggests that CHOL ratio is more highly correlated than LDH and protein ratios with the clinical diagnosis for exudates, which is significant at the 0.01 level. These results are similar to those obtained by Hamal et al. [12], who suggested that CHOL ratio is more highly correlated than protein ratio with the clinical diagnosis for exudate. Jiménez et al. [13] also reported that the highest diagnostic yield was observed with the combination of pleural cholesterol, pleural LDH, and the pleural fluid/serum protein ratio.

5. Conclusion

Based on the present study findings and a review of extant work in this field, it can be concluded that:

1. Analysis of the CHOL ratio in serum and effusion samples is the best diagnostic tool in the differentiation between exudative and transudate pleural effusions.
2. Tuberculosis is most frequently observed as a causative agent of exudative pleural effusion.
3. CHOL level in serum and effusion samples has a better sensitivity, specificity and positive predictive value in differentiating exudates and transudates than do LDH and protein levels in the same samples.

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