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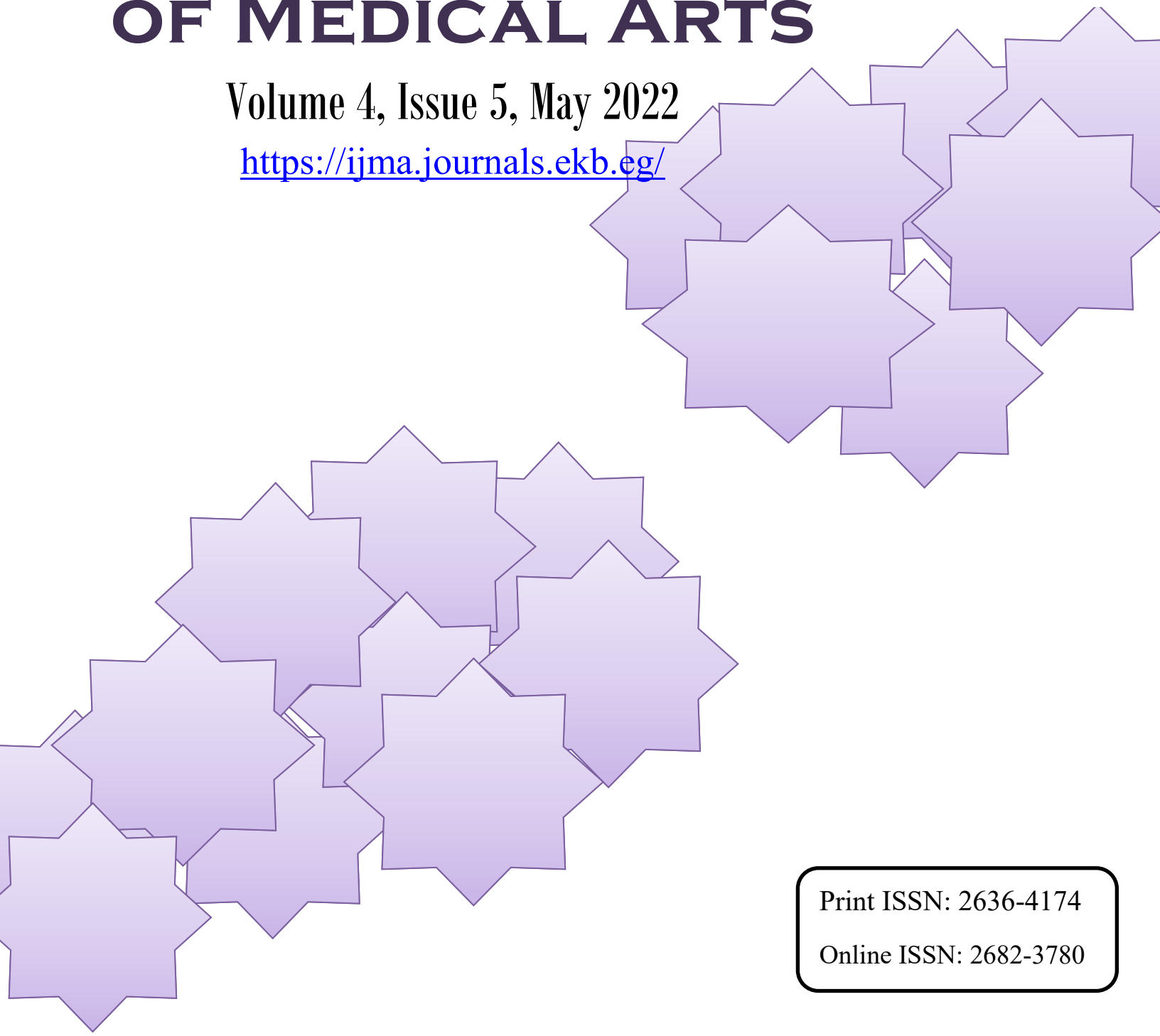

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Original Article

Combined Uric Acid and Cholesterol Pleural Fluid Levels as Biochemical Markers for Differentiation between Transudative and Exudative Pleural Effusions

Mahmoud Elsaeed Ahmed [1]*, Mohammad Essayed Abo-ghabsha[2]

[1] Department of Chest Diseases, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.

[2] Department of Clinical Pathology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.

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*Corresponding author

Email: mahmoudemara919@gmail.com

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ABSTRACT

Background: Pleural effusion results from an abnormal pathophysiological state of the equilibrium between pleural fluid formation and removal. Normally, pleural space contains about 10 ml of fluid on each side.

The aim of the work: To assess the sensitivity and specificity of combined pleural fluid uric acid and cholesterol level in differentiation between the transudative and exudative pleural effusions.

Materials and Methods: 54 patients with pleural effusion were included and divided into transudates, and exudates based on clinical, pathological, imaging and Light's criteria. In addition, uric acid and cholesterol levels in pleural fluid were measured.

Results: This study's mean pleural fluid cholesterol level was 90.97 ± 38.51 and 35 ± 5.63 mg/dl in exudates and transudates, respectively. They are statistically significant with sensitivity and specificity were 88% and 100%, respectively. The mean pleural fluid uric acid level in exudates and transudates was 4.08 ± 1.83 mg/dl and 5.86 ± 0.86 mg/dl, respectively and they are statistically significant. The optimum cut-off level for pleural fluid uric acid was 5.15 mg/dl with a sensitivity of 85% and specificity of 80%. The combined parameter of uric acid and cholesterol level in the pleural fluid gives a more powerful discriminating agent between exudative and transudative pleural fluids with sensitivity and specificity being 94.1% and 100%, respectively.

Conclusion: The combined parameter of the pleural fluid level of uric acid and cholesterol is of great value for distinguishing between transudative and exudative types of pleural effusions.

Keywords: Transudate; Pleural effusion; Exudates; Cholesterol; Uric acid.

INTRODUCTION

Pleural effusion has been defined as excessive accumulation of fluid in the pleural cavity. It results from an abnormal pathophysiological state of the equilibrium between pleural fluid formation and removal [1]. Since 1972, Light's criteria [2] are the traditional used criteria to discriminate between exudative and transudative pleural effusions using biochemical analysis of serum and pleural fluid [3,4].

Light *et al*. found criteria to have specificity and sensitivity of 98% and 99%, respectively, for differentiating between transudative and exudative pleural liquids. Lactate dehydrogenase LDH in pleural fluid to serum level is greater than 0.6, or LDH is more than 2/3 of upper normal limit for serum level, or pleural fluid protein to serum-level ratio is greater than 0.5 [5]. However, the other investigators reported only specificity of seventy to eighty percent with Light's criteria. Also, by Light's criteria, there is about 25% of patients with transudative type may be wrongly identified as exudative type, such as patients with heart failure received diuretic therapy [6]. Lucia *et al*., Addala *et al*. and Cornes *et al*. mentioned that, there is discordancy in a significant percentage of patients between the results of the pleural liquid analysis depending on Light's criteria and the final clinical diagnosis. Discordant exudates decrease the precision of Light's criteria to identify exudate pleural effusions, increasing the risk of misclassifying a transudate as an exudate [7-9].

Several trials have been searched to aid on the differentiation accuracy. They include the analysis of serum-pleural fluid albumin gradient [10], cholesterol level in pleural liquid [11], bilirubin ratios [12], and pleural fluid-to-serum cholinesterase ratio [13], pleural fluid uric acid [14], combined pleural liquid cholesterol and LDH [15].

Heffner and his colleagues, have reported that exudative liquid can be identified with one of these parameters [16]: Cholesterol in pleural liquid is greater than 45 mg/dL, protein in pleural liquid is more than 2.9 gm/dL, LDH in pleural liquid is more than two-third of upper normal limit of serum levels.

THE AIM OF THE STUDY

The aim of this study was to assess the sensitivity and specificity of combined pleural fluid uric acid and cholesterol level [as a new simplified method other than the traditional light's criteria] in differentiation between the exudative and transudative pleural effusions.

PATIENTS AND METHODS

This observational study included 54 patients with pleural effusion [33 males and 21 females] who admitted in the chest department, Bab Al Shearya University Hospital, from April 2021 to November 2021. The patients were divided in two groups: Group A - transudates, and Group B - exudates based on the etiology which has been identified by clinical, pathological evaluation, imaging, Light's criteria, and cholesterol in pleural fluid with a cut-off value of 45 mg/dL as reported by Heffner *et al*. [16].

Group: A [transudates]: This group comprised of 20 patients, twelve patients had liver cell failure and eight patients had heart failure. Group: B [exudates]: This group comprised 34 patients, shown in [table 1], two Patients had tuberculosis as a cause of pleural effusion, five patients with parapneumonic fluid or empyema, twenty patients had malignant pleural effusion, one patient with rheumatoid arthritis, one patient with pyo-pneumothorax and four patients with in determinant etiology. Patients, who had hemothorax secondary to trauma, were excluded from the study.

All fluid samples were examined for LDH, cell count, uric acid, protein, cholesterol, acid-fast stain, Gram stain, culture and cytology. Concomitant blood samples were performed and examined for chemical parameters as LDH, protein and uric acid. Other investigations, such as chest CT scan, bronchoscopy, and guided biopsies, were performed when needed to identify the etiology. The fluid was analyzed without centrifugation to determine uric acid, cholesterol and protein using colorimetric method using cobas c311 fully automatic analyzer [Roche diagnostic kits]. Uric acid was done by uricase/peroxidase method. Protein was assessed by biuret method. Cholesterol with Boehringer-Mannheim [cholesterol oxidase peroxidase] enzymatic method CHOD PAP.

The study was accepted and approved by the Ethical Committee of Faculty of Medicine, Al-Azhar University, and written consent was signed from each participant.

Statistical methodology: IBM Statistical Package for Social Science [SPSS]® version 26 has been used to conduct the statistical analysis. Baseline and clinical data comparisons were recorded using chi-square test with independent samples t-test for categorical and continuous data, respectively. All tests were performed at 0.05 level of significance. Receiver operating characteristic curves [ROC] were drawn to test and compare

different potential predictors of pleural fluid nature using area under the ROC curves. Discriminant analysis and binary logistic regression models were also used for building prediction models after ensuring model fitness.

RESULTS

Out of 54 cases studied, there were 34 cases of exudate pleural effusion of which 21 [61.8%] were men and 13 [38.2%] women with a mean age of 56 years [range 39–73]. There were 20 cases of transudative pleural effusion of which 12 [60%] were men and 8 [40%] women with a mean age of 62 years [range 52–72] [Table1]. In the current work, serum levels of LDH and serum total protein were significantly reduced in transudates than exudates. In addition, pleural fluid total protein, LDH and total cholesterol were also significantly reduced in transudate than exudate. However, serum uric acid was significantly increased in transudates than exudate. Finally, pleural fluid/serum ratio of total protein and LDH were significantly reduced while uric acid ratio was significantly increased in transudates than exudates [Table 2].

ROC curves of pleural uric acid and pleural/serum uric acid ratio are shown in [Figure1]. The best cut-off level was defined by selecting points of test values that provided the greatest sum of sensitivity and specificity. The optimal sensitivity and specificity of 85% and 80% to pleural uric acid level to predict transudate was achieved at a cutoff point of ≥ 5.15. However, at a cutoff point of 5.5, they were 75% and 80% respectively. Area under the ROC curve with 95% CI was 0.846 [0.74 – 0.95] and p-value of >0.0001. The optimum cut-off level for P/S uric acid ratio was 0.945 with sensitivity of 70% and specificity of 70.6% [Table 6 in supplementary data]. The area under the ROC curve with 95% CI is 0.764 [0.636 – 0.892].

A Collecting ROC curves for pleural/serum P/S protein ratio, P/S LDH ratio and pleural cholesterol are shown in [figure 2]. ROC curve for pleural/serum protein ratio [blue line] with a cut-off level more than 0.5, the sensitivity is 76.5% and specificity is 100%. Area under the ROC curve with 95% CI is 0.912 [0.822 – 0.991] and p-value ≤0.0001. The ROC curve for pleural/serum LDH ratio [red line] with a cut-off level more than 0.6, the sensitivity is 94.1% and specificity is 90%. Area under the ROC curve with 95% CI is 0.966 [0.922 – 1.000] and p-value ≤0.0001. The ROC curve for pleural level cholesterol [green line] with a cut-off more than 45, the sensitivity is 88.2% and specificity is 100%. Area under the ROC curve with 95% CI is 0.918 [0.83 – 1.000] and p-value ≤0.0001.

As shown in [table 3], Sensitivity and specificity of combined pleural uric acid and cholesterol as a predictor of exudative pleural effusion were 94.1% and 100%, respectively.

The optimal sensitivity and specificity of 85% and 80% to pleural uric acid level to predict transudate was achieved at a cut-off point of ≥ 5.15. However, at a cut-off point of 5.5, they were 75% and 80% respectively [Table 4, 5].

A cutoff value for uric acid ratio of 0.945 or higher to identify transudate, the sensitivity is 70% and specificity is 70.6% [Table 6].

Table [1]: Age, sex and etiology of pleural effusions

Factors	Transudates [n = 20]	Exudate [n = 34]
Age – Mean±SD	62.6±10.56	55.94±17.638
Sex – Number [%]	12[60]	21[61.8]
Etiology		
Adenocarcinoma	0	2[5.7]
Empyema	0	1[2.8]
Heart failure	8[40]	1[2.8]
Liver cell failure	12[60]	0
Lymphoma	0	1[2.8]
Mesothelioma	0	17[48.6]
Non-specific	0	4[11.4]
Parapneumonic effusion	0	4[11.4]
Pyopneumothorax	0	1[2.8]
Rheumatoid arthritis	0	1[2.8]
Tuberculosis	0	2[5.7]

Table [2]: Pleural fluid and serum estimation.

Factors	Transudates [n = 20]	Exudate [n = 34]	p-value
Serum labs:			
serum LDH	253.65±147.9	374.8±125.2	<0.0001*
Serum uric acid	5.44±0.88	5.36±1.94	0.86
serum total protein	6.11±0.51	6.87±0.81	<0.0001*
Pleural fluid labs:			
Pleural fluid total protein	2.41±0.49	4.19±1.02	<0.0001*
Pleural fluid LDH	117.75±65.85	810.1±744.02	<0.0001*
Pleural fluid uric acid	5.86±0.86	4.08±1.83	<0.0001*
Pleural fluid total cholesterol	35.00±5.63	90.97±38.51	<0.0001*
Pleural fluid/serum ratio:			
Total protein ratio	0.39±0.06	0.61±0.15	<0.0001*
Uric acid ratio	1.08±0.21	0.80±0.31	<0.0001*
LDH ratio	0.47±0.14	2.26±1.94	<0.0001*

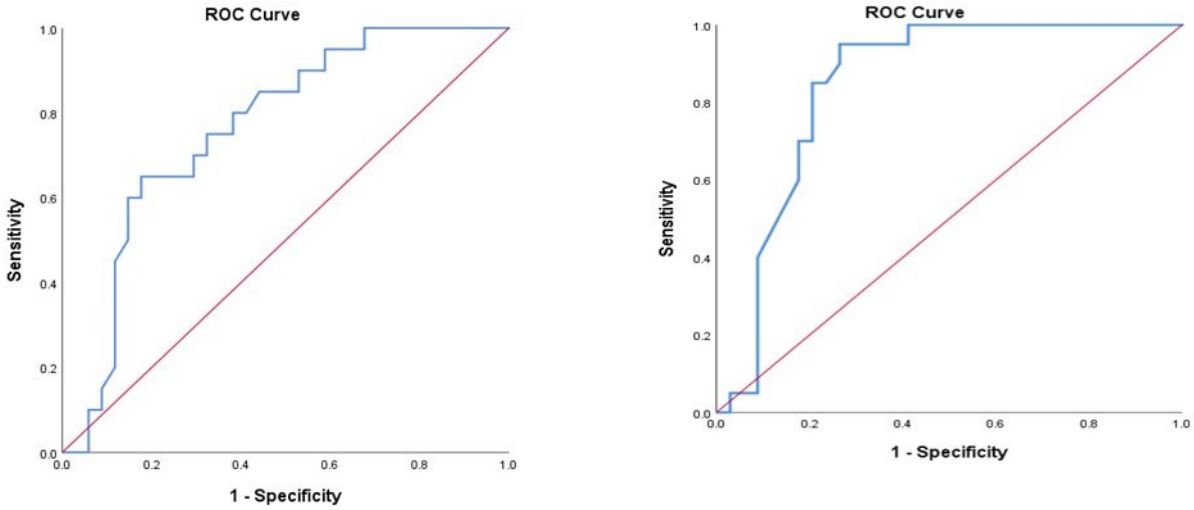

Figure [1]: ROC curves for pleural/serum uric acid ratio [on the left side] and pleural uric acid level [on the right side] as predictors of transudate with sensitivity and 1-specificity

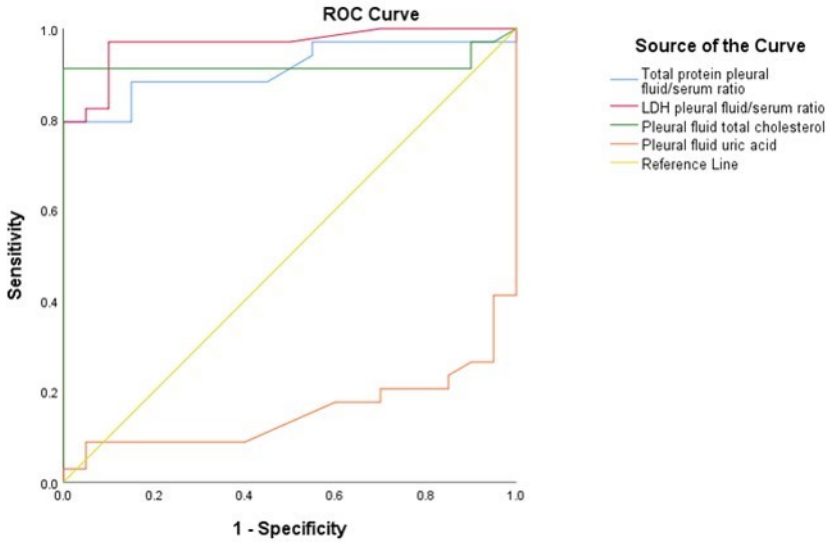

Figure [2]: ROC curves for P/S protein ratio, P/S LDH ratio and pleural cholesterol as predictors of exudate with sensitivity and 1-specificity

Table [4]: Pleural uric acid level as a predictor for transudate with sensitivity and 1- specificity for each cut-off point

Positive if ≥	Sensitivity	1 – Specificity
0.8000	1.000	1.000
1.9000	1.000	0.971
2.0500	1.000	0.941
2.1750	1.000	0.882
2.3750	1.000	0.853
2.5500	1.000	0.824
2.7500	1.000	0.794
3.0500	1.000	0.676
3.2500	1.000	0.618
3.4000	1.000	0.559
3.5500	1.000	0.529
3.7000	1.000	0.500
3.8500	1.000	0.471
4.0000	1.000	0.412
4.1500	0.950	0.412
4.2500	0.950	0.324
4.3500	0.950	0.265
4.6500	0.900	0.265
4.9500	0.850	0.235
5.1500	0.850	0.206
5.4000	0.800	0.206
5.5500	0.750	0.206
5.6500	0.700	0.206
5.7500	0.700	0.176
5.8500	0.600	0.176
6.0000	0.400	0.088

Table [5]: Prediction of exudate nature among pleural effusion patients from uric acid ratio using logistic regression

	Beta	S.E.	p-value	Adjusted OR
Age	-0.025	0.024	0.297	0.976
Female	-0.128	0.665	0.847	0.88
Uric acid ratio	-3.656	1.273	0.004	0.026*
Constant	5.518	1.906	0.004	249.2

Beta: Regression coefficient. SE : Standard error. Adjusted OR: Adjusted odds ratio. *: Significant p-value at 0.05 level of significance.The logistic regression model had Omnibus test *p*-value of 0.004, Hosmer and Lemeshow test *p*-value of 0.14, Nagelkerke R Square of 0.3, classification table of 76%, and area under the ROC curve of 0.79 [*p* <0.0001] as shown in figure [3].

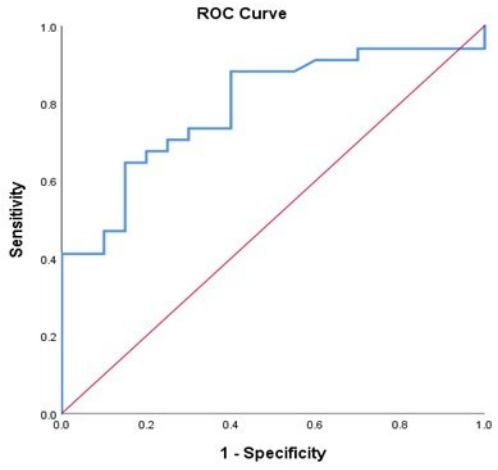

Figure [3]: ROC curve of logistic regression model of exudate prediction from uric acid ratio compared to transudate.

Table [6]: Uric acid ratio as a predictor for transudate with sensitivity and 1- specificity for each cut-off point.

Uric a ratio ≥	Sensitivity	1 - Specificity
0.65	1	0.676
0.695	0.95	0.676
0.71	0.95	0.647
0.725	0.95	0.588
0.735	0.9	0.588
0.755	0.9	0.529
0.78	0.85	0.529
0.795	0.85	0.5
0.81	0.85	0.471
0.83	0.85	0.441
0.845	0.8	0.412
0.86	0.8	0.382
0.885	0.75	0.382
0.91	0.75	0.324
0.93	0.7	0.324
0.945	0.7	0.294
0.96	0.65	0.294
0.98	0.65	0.265
1.005	0.65	0.235
1.025	0.65	0.206
1.05	0.65	0.176
1.1	0.6	0.176
1.135	0.6	0.147
1.145	0.55	0.147
1.155	0.5	0.147
1.18	0.45	0.118
1.21	0.35	0.118
1.225	0.3	0.118

Table [7]: Prediction of exudate nature among pleural effusion patients from pleural uric acid level using logistic regression

	Beta	S.E.	p-value	Adjusted OR
Age	-.004	.026	.888	.996
Female	.411	.706	.561	1.508
Pl uric acid level	-.767	.262	.003*	.464
Constant	4.397	1.663	.008	81.246

Beta: Regression coefficient. SE: Standard error. Adjusted OR: Adjusted odds ratio. *: Significant p-value at 0.05 level of significance.The logistic regression model had Omnibus test p-value of 0.002, Hosmer and Lemeshow test p-value of 0.163, Nagelkerke R Square of 0.33, classification table of 78%, and area under the ROC curve with 95% CI of 0.834 [0.72 – 0.95] [p <0.0001] as shown in figure [4].

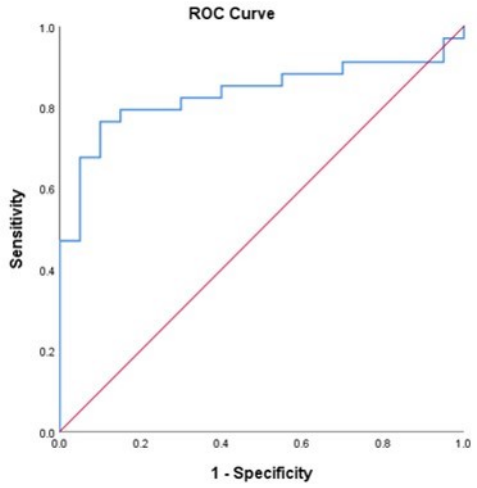

Figure [4]: ROC curve of logistic regression model of exudate prediction from pleural uric acid level compared to transudate.

DISCUSSION

The mean pleural liquid uric acid level in exudative type vs transudative one was 4.08 ± 1.83 mg/dl, 5.86 ± 0.86 mg/dl respectively and they were statistically significant. The mean pleural liquid/serum uric acid ratio in exudative type's vs transudates were 0.80 ± 0.31 and 1.08 ± 0.21 respectively and they were statistically significant.

The level of uric acid in this research increases with transudative type in comparative to exudative one. The reasons behind that have not been fully understood, in exudative type the factors leading to pleural fluid accumulation are due to increased capillary permeability and lymphatic occlusion. Whereas transudates are the result of changes occurred in hydrostatic elements [17].

Uzun and colleagues stated that uric acid might be present and increase in clinical situations accompanied by tissue hypoxia [18]. Patients with transudative effusion [such as heart failure or liver cirrhosis] had mostly oxidative stress that can explain the excess level of uric acid synthesis.

Muzaffar and colleagues stated that binding of plasma protein to uric acid is minimal and uric acid is freely diffuse to body compartments. They also suggested that the excess of uric acid levels in pleural liquid [transudative type] is due to changing in capillary pressure that might lead to increase fluid formation [19].

This study reveals an accepted discriminating power of pleural liquid uric acid between transudative type and exudative one with a sensitivity and specificity of 85% and 80% respectively when a cut off value of ≥ 5.15 mg/dl is considered, which is on line with the results reported by Uzun and colleagues [18] who had shown that the mean pleural liquid uric acid varies significantly between transudates [487.7±165 micromol/l] and exudates [279.9±142.1 micromol/l] with the specificity and sensitivity of pleural liquid uric acid for diagnosis of transudative effusions being 73% and 80%, respectively.

Also, in line with the results reported by Sutanto [20] who had mentioned that pleural fluid uric acid levels showed a sensitivity and specificity of 86% and 87%, with a cut-off of 7.25 for transudate results. Jain *et al*. elaborated an ideal cut-off level of 5.5 mg/dl for pleural liquid uric acid has a sensitivity of 94.0% with specificity of 83.0% to diagnose transudative effusion [21].

In this research, the mean pleural liquid cholesterol level in exudative type and transudative one was 90.97 ± 38.51 and 35 ± 5.63 mg/dl, respectively, and they were statistically significant with sensitivity and specificity were 88% and 100%, respectively. The combined parameter of uric acid with cholesterol level in the pleural liquid gives a more powerful discriminating agent between exudative and transudative pleural fluids with sensitivity and specificity were 94.1% and 100%, respectively.

Conclusions:

Simplified combined criteria of pleural liquid uric acid less than 5.15 and pleural cholesterol greater than 45 mg/dL can identify an exudate with an overall diagnostic accuracy and a sensitivity similar to that of Light's criteria. It also avoids simultaneous blood sampling, so reducing potential costs and patient discomfort.

Conflict of interest: none

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