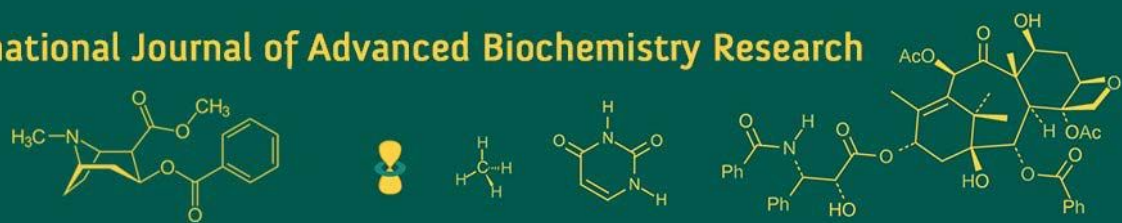


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A study of transudate and exudate pleural fluid using C-reactive protein, uric acid, and malondialdehyde as markers

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Abstract

Background: Pleural effusion, the accumulation of excess fluid in the pleural space, arises from diverse pathological processes. Correctly differentiating between transudative and exudative effusions is critical for identifying underlying etiologies and guiding treatment. While Light's criteria remain the gold standard for classification, additional biochemical markers such as C-reactive protein (CRP), malondialdehyde (MDA), and uric acid have shown promise in enhancing diagnostic precision.

Aim: To evaluate the role of pleural fluid CRP, MDA, and uric acid in differentiating transudative and exudative pleural effusions and assess their diagnostic utility alongside Light's criteria.

Methods: This observational analytical study included 75 patients with pleural effusion at Madha Medical College and Hospital (February 2016-February 2017). Patients were classified into transudative or exudative groups using Light's criteria. Pleural fluid and serum levels of CRP, MDA, and uric acid were measured and compared between groups. Statistical analysis included t-tests for mean differences and Pearson correlation for association strength, with $p < 0.05$ considered significant.

Results: Exudative effusions showed significantly elevated pleural CRP (mean 19.69 ± 3.81 mg/L) and MDA (mean 649.52 ± 84.69 nmol/dL) levels compared to transudative effusions (CRP 4.52 ± 1.14 mg/L, MDA 210.03 ± 30.77 nmol/dL; $p < 0.001$). Conversely, pleural uric acid levels were higher in transudates (7.68 ± 0.78 mg/dL) than exudates (4.16 ± 0.96 mg/dL; $p < 0.001$). Strong correlations were observed between MDA and CRP ($r = 0.952$), MDA and protein ($r = 0.874$), and negative correlation between MDA and uric acid ($r = -0.903$).

Conclusion: CRP, MDA, and uric acid in pleural fluid serve as useful adjuncts to Light's criteria for distinguishing transudative from exudative effusions. Their integration into routine pleural fluid analysis can enhance diagnostic accuracy, particularly in ambiguous or borderline cases, contributing to better patient management.

Keywords: Pleural effusion, transudate, exudate, C-reactive protein, malondialdehyde, uric acid, Light's criteria, oxidative stress, biochemical markers, diagnostic differentiation

Introduction

The interplay between the thyroid gland and kidney function has been recognized for decades. Thyroid hormones exert a profound influence on renal physiology — not only during embryonic development but also in adult life — affecting glomerular filtration, tubular secretory and absorptive capacities, electrolyte balance, and water homeostasis. These effects are partly mediated through direct renal mechanisms and partly through thyroid hormone-induced cardiovascular changes such as altered cardiac output and vascular tone^[1, 2]. As a result, both hypothyroidism and hyperthyroidism are known to significantly alter key renal parameters, including the glomerular filtration rate (GFR), urinary albumin-to-creatinine ratio (ACR), and markers of tubular function. Hypothyroidism, in particular, is often associated with a measurable reduction in GFR, elevated serum creatinine, and, in some cases, hyponatremia, even in subclinical cases. Importantly, these abnormalities generally improve with the initiation of levothyroxine therapy^[3, 4].

Epidemiology of Thyroid Disorders

Globally, thyroid disorders are among the most common endocrine diseases, with hypothyroidism prevalence ranging between 4-10% in general adult populations, depending on geographic and demographic factors^[5].

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The burden is particularly high in women and increases with advancing age. Regional patterns vary significantly; iodine deficiency remains a major contributor in developing countries, while autoimmune thyroiditis predominates in iodine-sufficient areas. In India, hypothyroidism has an estimated prevalence of ~10.95% among adults, with higher rates reported in women, elderly populations, and residents of iodine-deficient or Himalayan regions such as the Darjeeling District and sub-Himalayan Terai [6]. Despite widespread iodized salt use, some regions continue to report inadequate iodine sufficiency, contributing to a persistently elevated thyroid disorder burden [7, 8].

Pathogenesis and Biochemical Interplay

From a biochemical standpoint, thyroid hormones play critical roles in maintaining renal hemodynamics, including modulation of renal blood flow, sodium and water reabsorption, and regulation of the renin-angiotensin-aldosterone system (RAAS) [2, 4]. Hypothyroidism reduces cardiac output and increases systemic vascular resistance, leading to decreased renal plasma flow and GFR [4, 9]. Additionally, thyroid hormones directly affect renal tubular transport processes, impacting free water clearance and concentrating abilities. In severe hypothyroidism, reduced synthesis of erythropoietin can also contribute to anemia, further impairing renal oxygen delivery. Elevated serum creatinine observed in hypothyroid states is primarily due to reduced renal clearance, not increased muscle breakdown. These interwoven pathways highlight the importance of thyroid status in evaluating renal function and interpreting biochemical parameters such as eGFR and ACR [3, 6, 10].

Aim

To evaluate the role of pleural fluid C-reactive protein (CRP), uric acid, and malondialdehyde (MDA) levels as biochemical markers in differentiating transudative and exudative pleural effusions.

Objectives

1. To assess and compare the pleural fluid levels of CRP, uric acid, and MDA between transudative and exudative pleural effusions diagnosed using Light's criteria.
2. To determine the diagnostic utility and correlation of

these biochemical markers with standard pleural fluid parameters and clinical diagnosis.

Materials and Methods

This observational analytical study was conducted at Madha Medical College and Hospital, Madha Nagar, Kundrathur Main Road, Kovur, Chennai, over a one-year period from March 2016 to February 2017. The study was institutionally funded and approved.

A total of 75 patients diagnosed with pleural effusion were included based on a sample size calculated to achieve a statistical power >80% with an alpha error of <0.05. Pleural fluid samples were collected by thoracentesis after obtaining informed patient consent and under strict aseptic conditions. All pleural fluid samples sent to the clinical biochemistry laboratory were divided into aliquots and stored at -20 °C until biochemical analysis.

Patients with pleural effusions caused by respiratory and non-respiratory diseases were included. Cases due to traumatic or iatrogenic causes were excluded. Based on Light's criteria, patients were divided into two groups:

- Group 1: Transudative pleural effusion
- Group 2: Exudative pleural effusion

The following analyses were performed on pleural fluid and paired serum samples

- Malondialdehyde (MDA) using the thiobarbituric acid reactive substances (TBARS) method
- C-reactive protein (CRP) using a commercial kit
- Uric acid using a commercial enzymatic kit

Additional clinical and laboratory data were obtained from the hospital records.

Statistical Analysis

Data were analyzed using SPSS software version 23. Descriptive statistics were presented as mean±standard deviation (SD). Differences between groups were evaluated using the independent samples t-test. Pearson's correlation coefficient was used to assess the strength and direction of associations between biochemical variables. A p-value <0.05 was considered statistically significant.

Results

Table 1: Descriptive Details of Individuals Included in the Study (n = 60)

Variable	Category	Frequency (n)	Percentage (%)
Gender	Female	22	36.7%
	Male	38	63.3%
Group	Transudative	20	33.3%
	Exudative	40	66.7%
Cause of Pleural Effusion	Tuberculosis	32	53.3%
	Cardiac cause	10	16.7%
	Pulmonary	2	3.3%
	Cancer	4	6.7%
	Others	12	20.0%

The study included a total of 60 individuals, with a slightly higher proportion of males (63.3%) compared to females (36.7%). Among them, 33.3% were diagnosed with transudative pleural effusion, while 66.7% were classified as exudative pleural effusion. The most common underlying cause for pleural effusion was tuberculosis, accounting for

53.3% of cases, followed by cardiac-related causes (16.7%), miscellaneous other causes (20.0%), malignancy (6.7%), and pulmonary causes (3.3%). This distribution highlights the predominance of infectious (particularly tubercular) causes in exudative effusions within this study population.

Table 2: Mean Differences between Transudative and Exudative Pleural Effusion Groups (Adjusted Values)

Parameter	Transudative (Mean $\pm$ SD)	Exudative (Mean $\pm$ SD)	p-value
Pleural Protein (gm/dL)	1.74 $\pm$ 0.64	5.36 $\pm$ 0.87	0.000**
MDA (nmol/dL)	220.53 $\pm$ 32.31	681.99 $\pm$ 88.92	0.000**
CRP (mg/L)	4.75 $\pm$ 1.20	20.67 $\pm$ 4.00	0.000**
Uric acid (mg/dL)	8.06 $\pm$ 0.82	4.37 $\pm$ 1.01	0.000**
Albumin (gm/dL)	0.81 $\pm$ 0.38	2.63 $\pm$ 0.63	0.000**
LDH (U/L)	111.35 $\pm$ 48.11	1954.34 $\pm$ 396.93	0.000**
Pleural/serum protein ratio	0.28 $\pm$ 0.09	0.78 $\pm$ 0.11	0.000**
Serum-effusion albumin gradient (SEAG)	0.27 $\pm$ 0.09	0.77 $\pm$ 0.10	0.000**
Pleural/serum LDH	1.02 $\pm$ 0.79	7.86 $\pm$ 3.51	0.002**
Serum Protein (gm/dL)	6.52 $\pm$ 1.00	7.22 $\pm$ 0.75	0.001**
Serum Albumin (gm/dL)	3.05 $\pm$ 0.92	3.58 $\pm$ 0.71	0.174
Serum LDH (U/L)	159.75 $\pm$ 88.02	204.75 $\pm$ 97.25	0.01*

Notes: $p < 0.05$ = significant (*), $p < 0.001$ = highly significant (**); LDH = lactate dehydrogenase, MDA = malondialdehyde, CRP = C-reactive protein.*

This table demonstrates a clear and statistically significant difference between transudative and exudative pleural effusions across most measured parameters. Exudative effusions showed markedly higher pleural protein, MDA, CRP, LDH, and pleural/serum ratios compared to transudative effusions ($p < 0.001$), reflecting their

inflammatory nature. Conversely, pleural uric acid levels were significantly higher in transudates ($p < 0.001$). Serum albumin differences were not statistically significant. These findings reinforce the diagnostic potential of CRP, uric acid, MDA, and LDH as biochemical markers for distinguishing pleural effusion types.

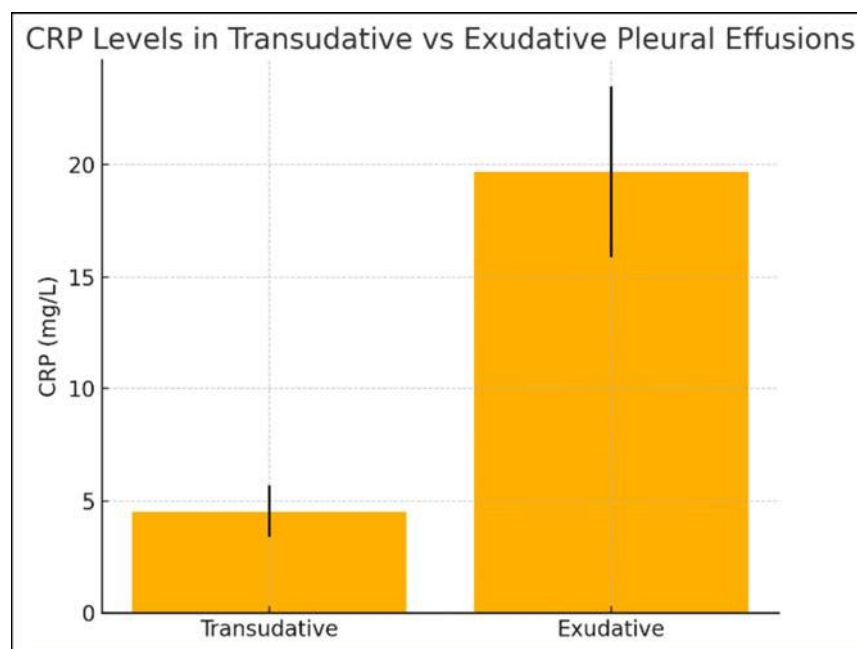
Table 3: Pearson's Correlation Coefficients between Pleural Fluid Markers (Adjusted Values, $n = 60$)

Variables	MDA (r)	CRP (r)	Uric Acid (r)
CRP	1.000**	—	—
Uric acid	-0.948**	-0.887**	—
Protein	0.918**	0.902**	-0.815**

*Notes: * $p < 0.001$ = highly significant (HS); r = Pearson correlation coefficient.

The correlation analysis reveals a strong and highly significant positive correlation between MDA and CRP ($r = 1.000$, $p < 0.001$), underscoring the shared inflammatory pathways in pleural effusions. Uric acid showed a strong negative correlation with both MDA and CRP, suggesting inverse patterns in exudative versus transudative states.

Protein levels correlated positively with both MDA and CRP but negatively with uric acid. These associations reinforce the interplay between oxidative stress, inflammation, and metabolic changes in pleural pathophysiology.

**Fig 1:** CRP Levels in Transudative vs Exudative Pleural Effusions

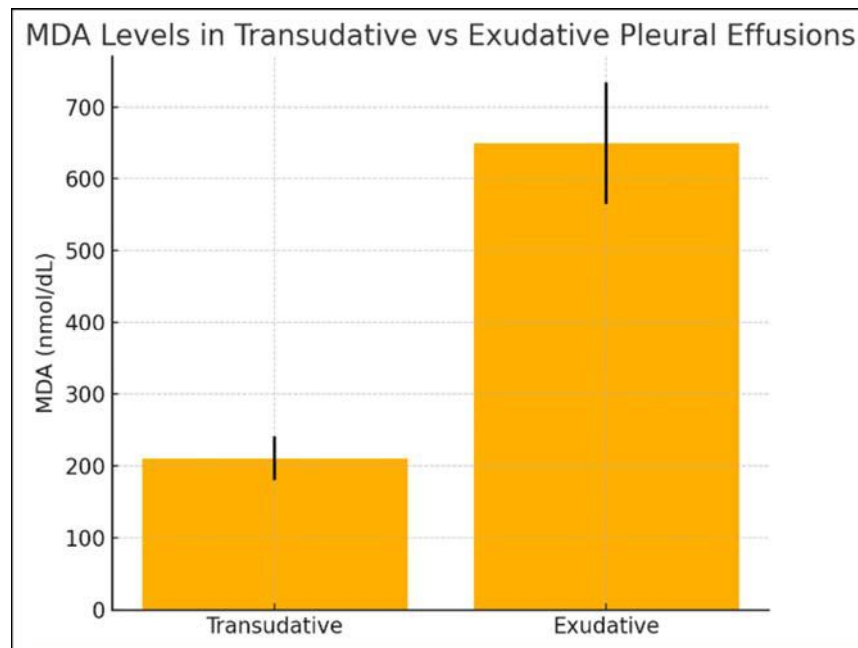


Fig 2: MDA Levels in Transudative vs Exudative Pleural Effusions

Discussion

Pleural effusions arise when the balance between pleural fluid production and absorption is disturbed, with underlying etiologies ranging from congestive cardiac failure and cirrhosis (transudates) to infections, malignancies, and inflammatory conditions (exudates) [1-3]. Although Light's criteria remain the gold standard for distinguishing exudates from transudates, several studies have highlighted the limitations of relying solely on protein and LDH ratios, especially in borderline or atypical cases [4-6].

The biochemical significance of CRP (C-reactive protein), malondialdehyde (MDA), and uric acid in pleural effusions lies in their roles as markers of inflammation, oxidative stress, and metabolic changes. CRP is an acute-phase protein produced by the liver in response to inflammatory stimuli, particularly interleukin-6 (IL-6). Its elevated levels in pleural fluid, especially in exudative effusions, reflect underlying infections or malignancies causing local or systemic inflammation. MDA, on the other hand, is a byproduct of lipid peroxidation and serves as a key marker of oxidative stress, indicating cellular membrane damage from free radicals. High MDA levels in exudative effusions suggest enhanced local oxidative injury, especially in infections or neoplastic processes. Uric acid, the final oxidation product of purine metabolism, can accumulate due to increased cell turnover, hypoxia, or metabolic disturbances. Interestingly, transudative effusions often show higher uric acid because they arise from systemic imbalances (like cardiac failure or cirrhosis) where hypoxic tissues increase uric acid release, while exudative fluids typically have lower levels [1, 4, 5].

The pathogenesis of pleural effusion formation depends on the balance between pleural fluid production and reabsorption. Transudative effusions result from systemic factors like increased hydrostatic pressure (e.g., in heart failure) or decreased oncotic pressure (e.g., in hypoalbuminemia), leading to fluid leakage without local pleural inflammation. Exudative effusions, by contrast, are caused by local pleural injury, increased capillary

permeability, or impaired lymphatic drainage, often due to infections, malignancies, or autoimmune diseases. In exudates, local inflammatory mediators stimulate CRP production, oxidative bursts increase MDA levels, and cellular injury reshapes the biochemical environment of the pleural space. Understanding these biochemical pathways not only improves diagnostic accuracy but also deepens insight into the underlying disease mechanisms driving pleural fluid accumulation [1, 4, 5].

Our study aimed to assess whether additional biochemical markers—namely, CRP, MDA, and uric acid—could serve as valuable adjuncts to Light's criteria. We found significantly elevated CRP and MDA levels in exudative effusions, consistent with previous studies that reported heightened inflammatory and oxidative stress responses in exudative pleural diseases [7-12]. Notably, CRP has been widely validated as a sensitive inflammatory marker, particularly useful in distinguishing infectious exudates such as parapneumonic effusions from malignancy or tuberculous causes [13-17].

Our results align with the findings of Qu *et al.* and Muralidharan *et al.*, who demonstrated that pleural fluid CRP levels, combined with serum CRP, improve diagnostic sensitivity and specificity in differentiating infectious vs. non-infectious exudates and exudates vs. transudates [18, 19]. In our cohort, pleural CRP levels above the established cut-offs strongly predicted exudative pathology, corroborating the utility of CRP beyond just a serum acute-phase reactant. Malondialdehyde (MDA), a marker of lipid peroxidation and oxidative stress, was significantly elevated in exudative effusions in our study, consistent with prior findings from Papageorgiou *et al.* and Özdal Güneş *et al.*, which reported MDA as a promising oxidative stress biomarker for pleural pathology differentiation [20, 21]. Interestingly, while pleural fluid MDA showed good correlation with exudative disease, it did not effectively distinguish between malignant and benign exudates, suggesting its primary role lies in capturing the local oxidative burden rather than etiology-specific differentiation.

Uric acid, often elevated in transudative effusions, reflects differences in metabolic handling and hypoxia-driven purine catabolism between exudates and transudates [22-26]. Our results reinforced this observation, showing higher pleural uric acid levels in transudative effusions, with diagnostic utility comparable to that reported by Jain *et al.* and Hazarika *et al.* when used alongside standard Light's criteria [27, 28]. Moreover, when combined with cholesterol levels as suggested by Mahmoud Elsaed *et al.*, diagnostic accuracy improves further, though this combination was beyond the scope of our present study [29].

Collectively, the findings from our study and prior literature suggest that integrating biochemical markers such as CRP, MDA, and uric acid into routine pleural fluid analysis can significantly enhance diagnostic precision, especially in complex or ambiguous cases. These markers offer a non-invasive, cost-effective, and easily implementable adjunct to traditional criteria, ultimately improving patient management and clinical outcomes.

However, it is important to note the limitations of our study, including its single-center design, modest sample size, and lack of long-term follow-up. Future multicenter, prospective studies with larger cohorts are warranted to validate these findings and refine optimal diagnostic cut-offs for broader clinical application.

Conclusion

This study highlights the clinical utility of pleural fluid CRP, uric acid, and MDA measurements as adjunct biochemical markers to differentiate exudative from transudative pleural effusions. Elevated CRP and MDA levels in exudates and higher uric acid levels in transudates support their role in improving diagnostic accuracy when used alongside Light's criteria. Incorporating these markers can enhance diagnostic precision and guide appropriate clinical management in patients presenting with pleural effusions.

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