Accurate and Rapid Diagnosis of Exudative Pleural Effusion
Therese Sobhy Ghatas\(^1\) MD; Moheb Wadea Elfaizy \(^1\) MD

**ABSTRACT**

**Background:** Accurate diagnosis of exudate pleural effusion is definitely important. Few studies have been published on this topic. The current work presents evidence for the importance of the pleural fluid markers like high sensitivity-C reactive protein (hsCRP); tumor necrosis factor alpha (TNF\(\alpha\)); and cholesterol levels measurement in differentiating types of exudative from transudative pleural effusion.

**Aim of The Work:** To determine and evaluate the diagnostic importance of measured levels of pleural fluid cholesterol, high sensitivity-CRP and tumor necrosis factor \(\alpha\) in diagnosing and differentiating transudate from exudate pleural effusion.

**Patient and Methods:** This study was conducted on 100 patients suffering from pleural effusion who subjected to diagnostic evaluation at Al Sahel Teaching Hospital. The full biochemical analysis of the pleural fluid, pleural fluid culture, and cytology examination were also performed. TNF \(\alpha\), hsCRP, and cholesterol level were assessed in the samples of pleural fluid.

**Results:** One hundred patients were initially evaluated, in accordance to Light's criteria, of 100 patients suffering from pleural effusion, 67 had exudative effusions while 33 patients had transudative pleural effusion. The concentrations of pleural fluid hsCRP and TNF \(\alpha\), found to be significantly elevated in the exudative nature group of pleural fluid than the transudative pleural effusion group (\(p < 0.05\)). Also, pleural fluid cholesterol level was elevated in the exudative pleural effusion than transudative pleural effusion (\(P<0.001\)).

**Conclusion:** Patients presented with pleural effusion, simple markers of elevated pleural fluid hsCRP, TNF\(\alpha\), and cholesterol levels may be helpful in discrimination between exudates and transudates effusion.

**Keywords:** Exudative; Pleural Effusion; Transudative.

**INTRODUCTION**

Pleural effusion incidence is about one million person every year. To diagnose and decide treatment plan for pleural effusions the fluid must be classified and differentiate into transudate or exudate effusion. If there is misdiagnosis severe complications may occur. The established criteria to differentiate exudates from transudates is only (Light's criteria). But results may be false positive or may occur in patients with transudative effusions when (Light's criteria) were applied.\(^1\)

The cholesterol level of pleural fluid can be used as a variable in diagnosing effusion of exudative nature and even can replace (Light’s criteria). Approaches to diagnose pleural effusion patients must be precise as multiple procedures depend on nature and analysis of the effusion fluid. Until present, no specific biochemical test is perfect alternative to (Light’s criteria).\(^2\)

The combinations of inflammatory markers of pleural fluid may be more clinically and diagnostically useful than the use of these markers separately.\(^3\)

Pleural (CRP) has recently been considered, as a valuable biological marker for the differentiation between exudate and transudate type pleural effusions and show higher specificity and sensitivity than serum level of CRP.\(^4\) (C reactive protein) is considered an appropriate marker due to its (1000) fold elevation in response to any infection and the presence of positive association between the pleural and serum level of CRP. However, there are few studies that were published on this topic.\(^5\)

High levels of (CRP) and tumor necrosis factor-alpha are seen in many inflammatory conditions such as infectious diseases, tissue injury and malignancy. Inflammatory responses result in pleural effusion of exudative nature.\(^6\)

This current study is aiming to evaluate the diagnostic importance of measured levels of cholesterol, high sensitivity-CRP and tumor necrosis factor- \(\alpha\) present in pleural fluid in differentiating exudate pleural effusion from transudate pleural effusion.

**PATIENTS AND METHODS**

This study was conducted between January 2019 and March 2020, on 100 patients attending to Al Sahel Teaching Hospital during the time of the study. The study included patients with pleural effusion diagnosed clinically and radiographically. The study was approved by the local ethics committee of...
Table 1: Patient Characteristics

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<th>Transudative Pleural Effusion Group</th>
<th>Exudative Pleural Effusion Group</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>33</td>
<td>67</td>
</tr>
<tr>
<td>Age</td>
<td>68.3 ± 9.1</td>
<td>51.2 ± 12.3</td>
</tr>
<tr>
<td>Gender F/M</td>
<td>18/15</td>
<td>35/32</td>
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hsCRP mean levels were 3.2 ± 1.1 mg/l in the transudative effusion patients and 14.3 ± 6.2 mg/l in exudative effusion patients. There was a statistically significant difference in the mean hsCRP levels between the two groups (p < 0.05). (Table 2). To determine the efficacy of pleural fluid hsCRP measurement in distinguishing between exudative and transudative effusions a cutoff value of > 5 mg/l was determined by standard ROC analysis. The sensitivity of hsCRP in differentiation between exudative and transudative pleural effusions based on this optimal cut off level was 95%. The specificity of exudative pleural effusion was 97%. The mean total TNFα level of exudative samples was 17.2 ± 8.7 ng/dl, which is significantly higher in comparison with the transudative group (p < 0.05) (Table 2).

The sensitivity and specificity of TNF α level in differentiating between exudates and transudates at a cut-off point of 12.9 ng/dl were 96% and 92%, respectively.
The mean level of cholesterol was 29±11.55 mg/dL in transudative pleural effusion versus 69.67±23.1 mg/dL in exudative pleural effusion. The cut-off value for pleural fluid CHOL level of ≥39 mg/dL had a sensitivity of 84% and specificity of 82%.

<table>
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<th>Table 2: Pleural Fluid Characteristics of The Study Population</th>
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<tr>
<td><strong>Transudative Pleural Effusion Group</strong></td>
</tr>
<tr>
<td>Protein</td>
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<tr>
<td>LDH</td>
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<td>hsCRP</td>
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<td>TNFα</td>
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<td>cholesterol</td>
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DISCUSSION

Several parameters like cholesterol level of pleural fluid and the ratio of pleural fluid to serum cholesterol level, value of the alkaline phosphatase, ratio of pleural fluid in relation to serum cholinesterase, and the ratio of pleural fluid in relation to bilirubin concentration of the serum have been proposed in differentiating the exudates from transudates fluid are more efficient than those of (Light’s criteria).7,8

In the current study, the diagnostic importance of cholesterol, [hsCRP][TNFα] level in the pleural fluid to discriminate exudate pleural effusion from transudate pleural effusion were evaluated. in exudate pleural effusion, these cholesterols and two acute phase response markers were significantly raised.

Is it valuable to depend on biochemical criteria for discrimination between exudative pleural effusions and transudative pleural effusions? The perfect answer to this important question has been successfully considered to be affirmative. But (Light’s criteria) did not supply appropriate discrimination between these diagnostic entities despite its high differentiating power. By application of (Light’s - criteria), about 15-30% of transudate pleural effusion are misclassified as exudate pleural effusion. Despite of the presence of unsuspected exudative pleural effusion, in cases receiving diuretic therapy, most patients show false exudative nature pleural effusion by (Light’s criteria) occur.9

The role of action of (CRP) is to bind phosphocholine and to detect foreign pathogens. Also, it can activate and stimulate the complement system by binding to its ligands and also can combine to phagocytic cells. Also, other pro-inflammatory effects are the activation of monocyte tissue factor and inflammatory cytokines. The changes in (CRP) levels reflect occurrence of inflammation and its extent and intensity and have been defined as a marker for the diagnosis and further management of different diseases. Although many previous studies have searched and investigated the levels of C reactive protein in various diseases, few studies have focused on its role and action in patients presented by pleural effusion.10

While pleural effusion levels of (C reactive protein) (not hsCRP) were estimated in other studies,11,12 in our study the evaluation was performed for the levels of high sensitivity (C reactive protein) [hsCRP] and gave outstanding results. Porcel in 2010 and his associates in 200913,14 evaluated CRP levels in pleural effusion and other several markers such as, interleukin-8, myeloperoxidase atrixmetallopeftainase-2, but not (hsCRP). They concentrated on parapneumonic effusion and tried to differentiate between both complicated and non-complicated parapneumonia.

Botana and his associates 201115 compared CRP pleural fluid levels in benign diseases such as infectious diseases and in malignant exudative pleural effusion. They also, compared with another previously related studies,16,17 they achieved different specificity and sensitivity which may be due to the assessment of high sensitivity-C reactive protein [hsCRP] instead of (C reactive protein) and they determining a different results and cutoff point.

In the current study results for measurement of pleural effusion levels of TNFα were in agreement with other previous studies,16,17 despite several discrepancies.18,21 However, these previous studies assessed pleural fluid levels of (TNF-α) just for only pleural effusions with underlying infectious disease.

According to the current study, the pleural fluid levels of hsCRP >5 mg/l and (TNFα) levels >12.9 ng/dl are valuable in discriminating transudative from exudative pleural effusion. (TNF-α), is an important mediator and regulator of the immune system response, showed high levels in both inflammatory and malignant exudative pleural effusion, compared to transudates.22

In the current study pleural fluid cut off point ≥39 mg/dL had a sensitivity of 84% and 82% specificity. This is in accordance with Hamal and his associates in 2013 who found that determination of pleural fluid cholesterol level is of great value in distinguishing between transudate and exudative pleural effusion.23

Yongchun and his associates in 2014 suggested that raised cholesterol level in pleural fluid associated with the presence of exudate pleural effusion, they stated that cholesterol contributes to the pathogenesis of exudate pleural effusion. It is not explained how this mechanism happens, so further research should investigate this question and provide a biological basis and explanation for this observation of association. They emphasized on the need to investigate the effect of cutoff value on the accuracy of diagnosis of the levels of pleural cholesterol. The values from 38 - 65 mg/dL. This variation in cutoff value reflects many differences in clinical context. A lower cutoff result is used for patients with cardiac problems presented with pleural effusion rather than for patients suffering from cancer. Further researches should direct to determine the cutoff value with optimal diagnostic accuracy.24
CONCLUSION

Pleural fluid level of HsCRP, TNFα, and cholesterol introduces beneficial diagnostic factors for differentiating exudates from transudates pleural effusion.

REFERENCES


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