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RESEARCH ARTICLE

Characterization of Markers in Blood Tests of Patients With Pleural Effusion and Their Correlation to Different Etiologies

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Abstract

Background: **To investigate the etiology of pleural effusion, a variety of examinations are performed, including invasive ones: Thoracentesis is an invasive procedure to remove fluid or air from the pleural cavity for diagnostic or therapeutic purposes. Until now, there are no blood markers that can help us diagnose the type of pleural effusion without the need for pleural puncture or drainage.**

Aims: **The aim of this study was to investigate the relationship and the utility of the new inflammatory markers taken from complete blood count (CBC) to differentiate between the various types of pleural effusion before the invasive procedure decision.**

Material and methods: **This is an observational retrospective study. Data was collected from medical records of patients aged 18-90 admitted in Ziv Medical Center, Safed, Israel that were diagnosed with pleural effusion from 2013 to 2019. Of those patients, of whom inflammatory markers from blood counts and thoracentesis results were obtained, the outcomes were compared with the diagnosis type of pleural effusion.**

Results: **This study involved 391 patients, 256 suffered from exudate type effusion, their median age was 72 years, while 135 suffered from transudate effusion, their median age was 80 years. Those with exudate effusion had higher levels of CRP, platelets, neutrophils, and lymphocytes in blood, whereas those with transudate effusion had higher levels of MPV and RDW in blood. Other blood markers such as NLR and PLR were not statistically significant, but were also higher in the blood of patients with exudate effusion.**

Conclusion: **An evaluation of simple and inexpensive measurements of blood count such as platelets, neutrophils, lymphocytes, MPV, RDW may provide insight into the etiology of pleural effusion.**

Keywords: Pleural effusion, Differential diagnosis, Inflammatory markers

1. Introduction

Pleural effusion (PE) is defined as excess fluid accumulation in the pleural cavity. There are two major classes of PE transudate pleural effusion (tPE), which is caused by systemic influences on pleural fluid formation or resorption, and exudates PE (ePE), caused by local influences on pleural fluid formation and resorption.

PE is a common clinical condition; its prevalence is estimated to be slightly higher than 500 cases per 100,000 inhabitants. Several causes can lead to PE, including diseases of the pleura, lung diseases, systemic diseases, organic dysfunction, or problems due to drug treatments.[1] To investigate the etiology of pleural effusion, a variety of examinations are performed, including invasive ones. Thoracentesis is an invasive procedure to remove fluid or air from the pleural cavity for both diagnostic or therapeutic purposes. Although thoracentesis is the gold standard for diagnosis, the information obtained by this method is limited, this invasive procedure has some limitations as and contraindicated in an uncooperative patient,

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severe hemostasis alteration, hemodynamic instability, severe respiratory failure or a pleural effusion considered too small to be safely taped, other relative limitations include cases in which the site of insertion has known bullous disease (e.g., emphysema) and the use of positive end-expiratory pressure (PEEP) and causes delays in the diagnosis and the initiation of appropriate therapy especially for infectious effusions, which may increase the rate of complications. Therefore, rapid diagnosis and determination of whether the cause of PE is infection would be of benefit. This may help avoid invasive examinations, thus enabling the quicker diagnosis of patients. Various serum biomarkers have therefore been investigated as methods for differentiating PE and their etiologies.

In this study, we aimed to investigate the correlation between the level of biomarkers in blood such as C-reactive protein (CRP), platelet-to-lymphocyte ratio (PLR), Neutrophil-lymphocyte ratio (NLR), Red cell distribution width (RDW), Mean platelet volume (MVP), and different etiologies of PE. We want to test if using regular blood tests can be useful in the diagnosis of PE.

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been assumed to be easily available and promising biomarkers in varius types of cancer.[2]

Neutrophil-lymphocyte ratio (NLR) has been investigated as a new inflammatory marker, as an index linked to lung disease, bacterial pneumonia and tuberculosis.[3]

Mean platelet volume (MPV), which can be measured from routine blood examinations, were associated to lung cancer patients, and their prognosis.[4]

C-reactive protein (CRP), whose circulating concentrations rise in response to inflammation. It is an acute-phase protein of hepatic origin that increases following interleukin-6 secretion by macrophages and T cells. Pleural effusion CRP levels are significantly higher in patients with empyema, parapneumonic effusion, and tuberculous effusion compared with patients who had malignant or transudate effusions.[5] Additionally, CRP levels were significantly lower in PE than in blood for all types of effusions.[5]

2. Material & methods

2.1. Study design

This is an observational descriptive retrospective cross-sectional study. We used medical charts of patients who have been diagnosed with pleural effusion, and for whom blood tests and thoracentesis were taken.

2.2. Subjects

The study includes 391 cases of patients aged 18–90 that were admitted to Ziv Medical Center due to pleural effusion from 2013 to 2019, from whom blood tests (CBC and chemistry) and thoracentesis results were obtained and an accurate diagnosis received.

Effusion type (exudate or transudate) was determined based on LIGHT criteria.[6] We measured LDH and protein levels in the blood and pleural effusion of all patients. Fluid is exudate if one of the following is present: Effusion protein/serum protein ratio greater than 0.5. Effusion lactate dehydrogenase (LDH)/serum LDH ratio greater than 0.6. Effusion LDH level greater than two-thirds the upper limit of the laboratory's reference range of serum LDH.

Demographic data, clinical signs of the disease, laboratory values of the disease, risk factors of the disease, imaging studies performed, complications of the disease and recurrence were described in the study. Complete blood counts were analysed in the haematology unit with a Beckman–Coulter Gen-S system device (Beckman–Coulter Inc., USA). MPV and RDW levels were gathered from patient's complete blood count, and NLR was calculated as the ratio of absolute number of neutrophil and lymphocyte counts. For each patient two consecutive blood tests were evaluated and checked for consistency of the parameters listed above, to exclude irregularities.

2.3. Sample size

To compare between two groups, assuming that the differences are relatively small, in effect size $D = 0.25$ and assuming that the size of the groups is equal, the significance level required was 5% with power of 80%, the required sample size was 398 patients.

2.4. Statistical analysis

Categorical variables were presented as frequencies and percentages and compared using the chi-squared test (Table 1). For continuous variables, summary tables were provided giving median data were presented as the median (Med) and 95% confidence interval (CI) and compared using Mann–Whitney non parametric tests since the data were not normally distributed according to

Kolmogorov–Smirnov test of normality (Tables 1 and 2). Receiver operating characteristic (ROC) curves were constructed to calculate the area under the curve (AUC) from each model, with 95% confidence interval (CI) (Fig. 1 and Table 3).

Statistical analysis was performed using SPSS 28 (IBM). A p-value less than 0.05 was considered to be statistically significant.

2.5. Ethical aspects

The research protocol was approved by the ethics committee of Ziv Medical Center, Safed, Israel.

Table 1. Demographic and background characteristics of the study patients according to group of pleural effusion.

Variables	Transudate (n = 135)	Exudate (n = 256)	p
Age, years (Med, [95%CI])	80 [75–79]	72 [66–70]	<0.001
Gender (n, %)			
Male	61, 45.2	128, 50.0	0.365
Female	74, 54.8	128, 50.0	
Ethnicity (n, %)			
Arab	37, 27.4	96, 37.5	0.045
Jewish	98, 72.6	160, 62.5	
Background diseases (n, %)			
Chronic heart failure	66, 48.9	14, 5.5	<0.001
Pneumonia	6, 4.4	43, 16.8	<0.001
Malignancy	4, 3.0	47, 18.4	<0.001
Empyema	0, 0	11, 4.3	0.019
Cirrhosis	4, 3.0	0, 0	0.014
Renal failure	3, 2.2	3, 1.2	0.669

Table 2. Blood and fluid tests characteristics of the study patients according to group of pleural effusion (Med, [95% CI]).

Variables	Transudate (n = 135)	Exudate (n = 256)	p[a]
CRP	19 [35–67]	68 [79–106]	<0.001
PLT	219 [209–246]	305 [316–354]	<0.001
Neutrophils	5.6 [5.9–7.2]	6.9 [7.7–9.0]	<0.001
Lymphocytes	1.1 [1.0–1.2]	1.3 [1.3–1.5]	<0.001
NLR	5.2 [6.3–9.6]	5.5 [6.6–10.2]	0.639
PLR	181 [220–324]	248 [274–329]	<0.001
RDW	16.2 [16.0–16.7]	15.1 [15.2–15.7]	<0.001
MPV	9.2 [9.1–9.6]	8.3 [8.4–8.8]	<0.001
LDH	231 [246–299]	215 [245–297]	0.029
PF LDH	79.7 [86.7–124]	232 [398–671]	<0.001
Protein	6.4 [6.1–6.5]	6.4 [6.3–6.5]	0.154
PF Protein	2.2 [2.1–2.4]	4.1 [3.9–4.2]	<0.001
Effusion leukocytes	370 [371–583]	1100 [620–12,591]	<0.001
pH - blood	7.36 [7.35–7.38]	7.39 [7.38–7.40]	<0.001
pH - Effusion	7.50 [7.49–7.58]	7.42 [7.26–7.41]	<0.001

Med - Median, CI - confidence interval, CRP–C reactive protein, PLT-platelets, NLR-neutrophils lymphocytes ratio, PLR-platelets lymphocytes ratio, RDW- Red Blood Cell Distribution Width, MPV- mean platelet volume, LDH- lactate dehydrogenase.

[a] Mann–Whitney non parametric test.

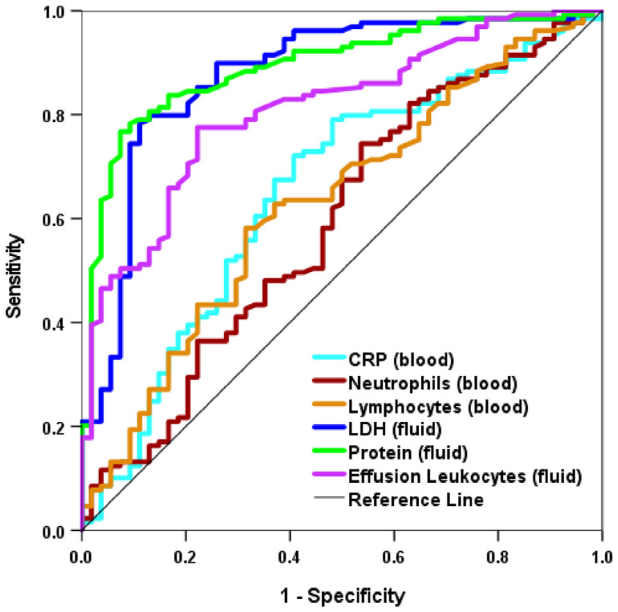

Fig. 1. ROC curves for 6 main blood and fluid tests in patients from whom a pleural effusion was taken.

Table 3. Receiver operating characteristic (ROC) curves for the test variables - Area under the curve (AUC) and 95% confidence interval (CI).

		AUC	95% CI	p
Blood	CRP	0.65	0.56–0.74	0.001
	Neutrophils	0.59	0.50–0.69	0.049
	Lymphocytes	0.63	0.54–0.72	0.006
	Combined	0.68	0.61–0.75	<0.001
Fluid	LDH	0.88	0.82–0.94	<0.001
	Protein	0.89	0.85–0.94	<0.001
	Effusion leukocytes	0.81	0.75–0.88	<0.001
	Combined	0.82	0.76–0.88	<0.001

3. Results

Table 1 shows several characteristics of the 391 patients recruited to the current study, from which 256 (65%) were patients with exudate and 135 (35%) were patients with transudate. The median age of the transudate group was statistically higher, (80 years old vs. 72 respectively, $p < 0.001$). Regarding the patients' background diseases, the prevalence of Pneumonia, Malignancy and Empyema were higher in the exudate group compared to the transudate group (11, 4.3, $p = 0.019$). An opposite trend was observed in the prevalence of Chronic heart failure and Cirrhosis.

Table 2 shows the median [95% CI] blood count and fluid tests collected from all patients and according to type of pleural effusion. CRP, PLT, Neutrophils, Lymphocytes, PLR, PF LDH, PF Protein, Effusion leukocytes and pH-blood were all statistically higher in the exudate group compared to the transudate group ($p < 0.001$), while RDW, MPV,

LDH and pH - effusion were higher in the transudate group compared to the exudate group ($p < 0.05$).

Fig. 1 and Table 3 compare the diagnostic performance of six different classifiers according to their AUC and 95% CI. Fluid tests (LDH, PF protein and effusion leukocytes) were found to be better classifiers compared to the blood classifiers (AUC = 0.88, 0.89, and 0.81 respectively, $p < 0.001$).

4. Discussion

According to the study's main results, 391 patients with pleural effusion participated.

Patient age distribution: Patients with the transudate effusion have an average age of 77.2, while patients with the exudate effusion have an average age of 67.6.

Considering that the transudate effusion is mainly due to heart failure disease, this finding is appropriate for older patients.[7] By contrast, exudate-type effusion characterizes malignant and infectious diseases, which correspond with younger patients.[8]

As seen in this study, there were more patients with exudate effusion recruited. Recruitment for this position was arbitrary. However, it resulted from a research preliminary, anticipated bias.

Since many patients with transudate effusion have a known diagnosis of chronic heart failure, and therefore they do not undergo pleural puncture analysis, this work does not include them.

In accordance with our research expectations, most patients who presented transudate effusion had been diagnosed with chronic heart failure disease, while most patients who presented exudate effusion suffered from infectious diseases such as pneumonia, or various malignancies.[9,10]

Blood tests showed that for exudate-type effusion, the inflammation index **CRP** was significantly higher than for transudate-type effusion. This is consistent with our expectations because exudate effusion indicates inflammatory condition, such as infection or malignancy, so it is to be expected.[11]

Similarly, **platelets** were significantly higher in exudate-type effusion. As known and in accordance to our expectations, increased platelet count is a well-known marker of adverse outcome in patients diagnosed with pneumonia.[12]

Therefore, we expected to find a large number of platelets in the exudate-type pleural effusion, compared to the transudate-type effusion.

The **neutrophil** and **lymphocyte** counts were higher in the exudate effusion as well, and these two indices are known to indicate an inflammatory condition, so the results are consistent with our expectations.

Having a high percentage of neutrophils in the blood is called neutrophilia. This is a sign that the body has an infection. Neutrophilia can point to a number of underlying conditions and factors, including infection, most likely bacterial.

High lymphocyte blood levels indicate that the body is dealing with an infection or other inflammatory condition.[13]

Mean platelet volume (MPV), which is normally associated with malignant pleural effusion, would be expected to appear more in exudates, which are typical of lung malignancies. However, our results show that MPV is higher in transudates.

Low MPV is actually linked with a worse prognosis of lung malignancies and, as such, may have been higher in transudate type effusion.[4]

High MPV is also linked to cardiac pathologies, including heart failure.[14]

Red cell distribution width (RDW) is strongly associated with multiple cardiopulmonary conditions including pulmonary arterial hypertension, congestive heart failure, and chronic pulmonary heart disease.[15]

Since these medical conditions are characterized by a transudate pleural effusion, the results of the study match our expectations since the RDW was found to be higher in the transudate type.

Based on known literature, **NLR** is an index of inflammation associated with lung diseases, bacterial pneumonia, and tuberculosis.[3]

Although not conclusive, our results are consistent with our hypothesis-that this index will be high in exudate-type effusion, which is associated with these diseases.[16]

Furthermore, NLR and PLR are also poor indicators of prognosis in various cancers.[17,18]

This finding is consistent with our results, as high NLR and PLR are associated with exudate-type effusions caused by lungs malignancies.

Various etiologies, such as empyema, malignancies, collagen disease, tuberculosis, hemothorax, and esophageal rupture have a low pH of pleural effusions.[16] Those diagnoses are characterized by the presence of exudate-type effusion.

One study have showed that serum calprotectin and NGAL were adjuvant serological markers for CPPE (complicated parapneumonic effusions) and empyema diagnosis.[18]

Our study actually showed the opposite result regarding the pH measured in the blood of a patient suffering from an exudate-type effusion: the pH in the blood of the patient suffering from an exudate-type effusion was higher than that of a patient who suffered from a transudate-type effusion.

It is difficult to discuss this finding's diagnostic significance since there is little information in the literature regarding this, moreover, the results obtained are not statistically significant. It is important to mention that acid-base disorders will affect the blood pH and supersede any effect from the pleural effusion itself.

In conclusion, our work has proven that it is possible to differentiate between exudate and transudate effusion by using a few inexpensive markers taken from patients' blood counts, and think about appropriate causes accordingly. PLT, neutrophils, and lymphocytes with higher counts are more suitable for exudate-type effusions. MPV and RDW of high values are suitable for transudate-effusion types.

PLR and NLR results were not statistically significant, but both were higher in a blood count of patients with exudate effusion. It is recommended to refer to the recently published guideline regarding pleural effusion strategies.[19,20]

We tried to avoid selection bias by selecting all patients admitted due pleural effusion, without sampling according to other parameters.

We tried to avoid information bias by working in an organized and thorough manner when processing the data. We had no influence on how the samples were taken and the tests performed but we can assume that most of the tests were done properly.

We believe that approximately 391 patients are sufficient to prove the validity of the results, so this amount was decided to represent the sample.

Ethics information

The research protocol was approved by the ethics and Helsinki committee of Ziv Medical Center, Safed, Israel.

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Conflict of interest

All authors of this manuscript have no conflict of interest.

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