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Chest

Diagnostic Value of Neutrophil-Lymphocyte Ratio in Exudative Pleural Effusion

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ABSTRACT

Background: As many patients may be unfit to undergo medical thoracoscopy, in addition to the low yield of closed pleural biopsy in malignant conditions, finding novel hematological or pleural fluid biomarkers to unmask the diagnosis of exudative pleural effusion and guide management plan becomes of increasing importance.
Aim of The Work: To assess the role of neutrophil to lymphocyte ratio in either blood or pleural fluid as a simple biomarker in detecting the underlying etiology of exudative pleural effusion.
Patients and Methods: This cross sectional study took place at Bab Al-Sha'reia University Hospital in the period between February 2021 and February 2022. It included 100 patients with exudative pleural effusion according to Light's criteria. Patients were divided according to the underlying cause into three groups; 1) malignant pleural effusion group, 2) tuberculous pleural effusion group and 3) para-pneumonic effusion group.
Results: The mean pleural fluid neutrophil to lymphocyte ratio was significantly lower in tuberculous pleural effusion group compared with other groups. As well, the same ratio was significantly lower in malignant pleural effusion group than para-pneumonia effusion group ($p < 0.001$). Similar findings were met when comparing the means of hematological neutrophil to lymphocyte ratio among the three studied groups.
Conclusion: Neutrophil to lymphocyte ratio in either blood or pleural fluid is an easily-obtained and cost-effective biomarker which can differentiate between malignant pleural effusion, tuberculous pleural effusion and para-pneumonic effusion.

Keywords: *Neutrophil; lymphocyte ratio; Exudative; pleural effusion.*

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INTRODUCTION

Pleural effusion is a widespread clinical condition, and its differential diagnosis may be troublesome requiring numerous investigations, including invasive maneuvers [1].

The gold standard for diagnosis of para-pneumonic effusion is the detection of a micro-organism in the pleural fluid (PF). Regrettably, about 40% of aspirated fluids are negative in ordinary cultures[2], but this outcome is increased when blood culture bottles are used simultaneously.[3]

Diagnosis of tuberculous pleural effusion (TPE) relays on positive smear and/or culture of Mycobacterium tuberculosis in (PF) or biopsies.[4] However, reaching the diagnosis could be opposed by many facts; 1) less than 10% of (TPEs) are AFB positive by direct smear, 2) liquid media cultures of (TPE) have a yield of about 45% only and 3) reported sensitivity for Xpert Ultra PCR on (TPE) is low (38-75%).[5]

Diagnosis of malignant pleural effusion (MPE) depends on positive PF cytology or pleural biopsy. Unluckily, the cytology outcome is almost 60%, and it is rarely to obtain positive results beyond the second trial of PF sampling.[6]

Many studies have checked biochemical markers to aid in the diagnosis of exudative pleural effusion, and some of them had scored some clinical viability.[1] Recently, neutrophil to lymphocyte ratio (NLR) has been tested as a new inflammatory marker.[7] and few studies used its value in pleural fluid for the differentiation between various etiologies.[8]

This work aimed at assessing the role of (NLR) in either blood or pleural fluid as a simple biomarker in detecting the underlying etiology of exudative pleural effusion.

PATIENTS AND METHODS

This cross sectional study took place at Bab Al-Sha'reia University Hospital in the period between February 2021 and February 2022. It included 100 patients diagnosed to have exudative pleural effusion according to Light's criteria.[9]

Exclusion Criteria

Patients were totally excluded from the study if they had any of the following conditions; transudative pleural effusion according to Light's criteria, minimal amount of pleural effusion that could not be safely sampled under ultrasound guide, undiagnosed exudative pleural effusion after performing all investigations including pleural tissue biopsy, missing data and refusal to participate in the study.

Clinical Data and Diagnostic Work-up

At the time of being included in the study, all patients were not diagnosed yet. Patients were submitted to detailed history taking, thorough clinical examination, routine laboratories including: complete blood count (CBC), liver and kidney function tests, random blood sugar (RBS) and coagulation profile (PT, APTT and INR). Plain chest x-ray (PA and lateral views) and chest computed tomography (CT) were performed to all participants. After that, diagnostic work-up for unexplained exudative pleural effusion was performed to all cases through ultrasound guided diagnostic thoracentesis to collect a fluid sample for: chemical analysis to confirm the exudative nature according to Light's criteria (pleural total protein to serum total protein ratio > 0.5, pleural LDH to serum LDH ratio >0.6 and pleural LDH level >2/3 upper limit of the laboratory reference range of serum LDH), differential leucocytic count, examination for acid-fast bacilli, culture for Gram positive and negative micro-organisms and cytology for malignant cells in pleural fluid (if needed). Tissue biopsies were taken via medical thoracoscopy or closed pleural biopsy when all previous investigations failed to show up a definite diagnosis.

Medical Thoracoscopy Technique

The procedure was done in the Interventional Pulmonology Unit by the hands of skillful pulmonologists. Each patient was located in the lateral position, with the side of the effusion directed upward, and his/her ipsilateral arm elevated above head to widen the intercostal spaces. Under the guide of ultrasound, the optimal site for intervention was chosen. After proper skin preparation and draping with povidone iodine 10%, about 10-15 cc of local anesthesia (lidocaine 2%) were injected at the site of entry, followed by conscious sedation by intravenous medazolam. Single incision (1-1.5 cm length) was done, and blunt dissection was performed to reach the parietal pleura. The pleura was pierced by a metal tocar, and the pleural fluid was aspirated using a suction catheter. A rigid thoracoscope of 7 mm diameter (Karl Storz Endoscope; Karl Storz; Tuttlingen, Germany) was introduced inside the pleural cavity to visualize it, and multiple biopsies were obtained from suspicious lesions. An intercostal tube was left to allow further drainage of residual and re-accumulated pleural fluid [10]. Heart rate, respiratory rate, oxygen saturation (SO_2) and arterial blood pressure were all closely monitored throughout the procedure. Oxygenation via nasal cannula (1-6 L/m) was applied to maintain SO_2 above 90%.

Closed Pleural Biopsy Technique

The maneuver was performed in a well-equipped room by well-trained chest physicians. The patient was asked to adopt sitting position, with his/her arms leant on a table at shoulder level, the site of entry (usually located at the dorso-lateral thoracic wall) was determined by the aid of ultrasonography. Under complete aseptic conditions, 5-10 cc of local anesthesia (lidocaine 2%) were applied, a 3-5 mm incision was made on the skin and subcutaneous tissues, and the Abram's needle was withdrawn in a rotating manner with steady pressure through the incision to traverse the subcutaneous tissues and intercostal muscles above the superior border of the inferior rib, so as to escape damaging the intercostal neurovascular bundle. On passing to the pleural cavity, the notch of the needle trocar was engaged to the pleura, and the required tissue sample was cut off and taken. This process was recurred several times to get sufficient tissue biopsies (usually 4-8 biopsies).[11]

Categorization of Patients According to Diagnosis

Following establishing diagnoses, patients were divided according to the underlying cause into three groups; 1) malignant pleural effusion group, 2) tuberculous pleural effusion group and 3) para-pneumonic pleural effusion group. Finally, neutrophil to lymphocyte ratios were determined in both blood (using parameters of CBC done on presentation) and pleural fluid for all patients, and the means were compared among different groups.

Ethical Considerations

The study was approved by the Ethical Committee of Al-Azhar University. All participants signed an informed written consent to share in the study.

Statistical Analysis

Data were analyzed using Statistical Program for Social Sciences (SPSS) version 24 (IBM corp., Armonk, NY, USA). Numerical data were expressed as mean ± standard deviation (SD), whereas qualitative data were expressed as frequency and percentage. Kruskal Wallis (KW) test was applied to compare the abnormally distributed data among the study groups. Tukey's post-Hoc was used to define means that are significantly different from each other, after (KW) test had showed a statistically significant relationship. P-values <0.05 were considered significant, whilst those <0.001 where considered highly significant.

RESULTS

Demographic data		Groups		
		MPE n= (48)	TPE n= (27)	PPE n= (25)
Age (years)	Mean	61.95	37.14	44.2
	±SD	9.88	12.89	14.59
Sex	Male	28 (58.3%)	16 (59.3%)	14 (56%)
	Female	20 (41.7%)	11 (40.7%)	11 (44%)
Smoking	Non-smoker	27 (56.3%)	18 (66.7%)	17 (68%)
	Smoker	16 (33.3%)	8 (29.6%)	8 (32%)
	Ex-smoker	5 (10.4%)	1 (3.7%)	0 (0%)
Asbestos exposure	Yes	37 (77.1%)	5 (18.5%)	7 (28%)
	No	11 (22.9%)	22 (81.5%)	18 (72%)

MPE: malignant pleural effusion, TPE: tuberculous pleural effusion, PPE: para-pneumonic effusion, SD: standard deviation.

Table (1): Demographic data distribution among studied groups

The patients of (MPE) group were the eldest with a mean age of (61.95±9.88) years, followed by (PPE) group (44.2±14.59) years, while (TPE) group patients were the youngest (37.14±12.89) years. Male sex was predominant in all study groups accounting for (58.3%, 59.3% and 56%) in (MPE), (TPE) and (PPE) groups respectively. The majority of (MPE) group (77.1%) had an occupational and/or resident (Shobra El-Kheima or Helwan) history of exposure to asbestos fibers (Table 1).

Malignant pathological pattern (n=48)	n (%)
Malignant mesothelioma	40 (83.33)
Malignant metastatic adenocarcinoma	5 (10.4)
Metastatic sqamous cell carcinoma	2 (4.18)
Metastatic lymphoma	1 (2.09)

Table (2): Malignant pathological pattern distribution in MPE group

Malignant mesothelioma was the responsible cause in (83.33%) of the (MPE) group, followed by metastatic adenocarcinoma (10.4%), Metastatic squamous cell carcinoma (4.18%) and finally metastatic lymphoma (2.09%) (Table 2).

Clinical data		Groups	Groups	Groups
		MPE n= (48)	MPE n= (48)	MPE n= (48)
Symptoms				
	Dyspnea	45 (93.8%)	6 (22.2%)	11 (44%)
	Chest pain	26 (54.2%)	11 (40.7%)	10 (40%)
	Cough	17 (35.4%)	14 (51.9%)	16 (64%)
	TM	11 (22.9%)	10 (37%)	13 (52%)
	Hemoptysis	2 (4.2%)	3 (11.1%)	2 (8%)
	PS	2 (4.2%)	0 (0%)	0 (0%)
Side of effusion				
	Right	28 (58.3%)	13 (48.1%)	13 (52%)
	Left	20 (41.7%)	10 (37%)	10 (40%)
	Bilateral	0 (0%)	4 (14.9%)	2 (8%)

MPE: malignant pleural effusion, TPE: tuberculous pleural effusion, PPE: para-pneumonic effusion, TM: toxic manifestations, PS: pressure symptoms.

Table (3): Clinical data distribution among studied groups

Dyspnea and chest pain were more prominent among patients of (MPE) group. Cough and toxic manifestations were more frequent in (PPE) group patients. Hemoptysis existed more in (TPE) group compared with other groups, while pressure symptoms were confined to (MPE) group. The right side was more frequently affected than the left side in all study groups, whereas bilaterality was more evident in (TPE) group (Table 3).

Pleural fluid parameters		Groups			KW	P	P1	P2	P3
		MPE n= (48)	TPE n= (27)	PPE n= (25)					
TLC/mm^3	Mean	4636.45	4267.77	10457.2	32.08	<0.001**	0.52	<0.001**	<0.001**
	±SD	2284.8	2312.76	5331.17					
Neut. /mm^3	Mean	1614.63	603.78	7000.93	66.97	<0.001**	<0.001**	<0.001**	<0.001**
	±SD	1038.36	289.41	3831.11					
Neut.%	Mean	34.02	15.62	70.44	74.62	<0.001**	<0.001**	<0.001**	<0.001**

	±SD	10.3	6.17	17.01					
Lymph./mm^3	Mean	2778.73	3499.96	3065.02	5.88	0.052	-	-	-
	±SD	1452.54	2025.13	3481.37					
Lymph.%	Mean	61.04	80.4	25.88	75.22	<0.001**	<0.001**	<0.001**	<0.001**
	±SD	10.12	6.11	17.04					
	±SD	2.8	1.93	1.64					
NLR	Mean	0.62	0.2	7.49	74.23	<0.001**	<0.001**	<0.001**	<0.001**
	±SD	0.41	0.1	12.04					
TP (gm/dl)	Mean	4.74	5.15	4.67	10.09	0.006*	0.0057*	0.61	0.0045*
	±SD	0.78	0.45	0.57					
LDH (IU/L)	Mean	498.5	520.22	754.48	15.77	<0.001**	0.55	<0.001**	0.0032*
	±SD	158.08	173.78	298.88					

MPE: malignant pleural effusion, TPE: tuberculous pleural effusion, PPE: para-pneumonic effusion, KW: Kruskal Wallis test, P1: p-value calculated by Tukey's post-Hoc test between malignant and tuberculous groups, P2: p-value calculated by Tukey's post-Hoc test between malignant and para-pneumonic groups, P3: p-value calculated by Tukey's post-Hoc test between tuberculous and para-pneumonic groups, SD: standard deviation, *: statistically significant, **: statistically highly significant, TLC: total leucocytic count, Neut.: neutrophils, Lymph.: lymphocytes, mm3: cubic milliliter, NLR: neutrophil to lymphocyte ratio, TP: total protein, LDH: lactate dehydrogenase, -: Tukey's post-Hoc test could not be applied due to non-significant p-value calculated by Kruskal Wallis test.

Table (4): Pleural fluid parameters distribution among studied groups

The mean pleural fluid total leucocytic count (TLC) was significantly higher among the patients of (PPE) group compared with other groups (p <0.001). The mean neutrophils count and percentage in pleural fluid were greatly higher in (PPE) group compared with the other groups (p <0.001). In turn, the same count and percentage were significantly lower in (TPE) group compared with (MPE) group (p <0.001). The mean lymphocytes percentage in pleural fluid was significantly higher in (TPE) group compared with others (p <0.001). Likewise, this percentage was also higher in (MPE) group compared with (PPE) group (p <0.001). The mean lymphocytes count in pleural fluid did not differ significantly among the study groups (p= 0.052). The mean pleural fluid neutrophil to lymphocyte ratio (NLR) was significantly different among the three studied groups (p <0.001), being lowest in (TPE) group (0.2±0.1), intermediate in (MPE) group (0.62±0.41) and highest in (PPE) group (7.49±12.04) (Table 4).

Peripheral blood parameters		**Groups**			**KW**	**P**	**P1**	**P2**	**P3**
		MPE n= (48)	TPE n= (27)	PPE n= (25)					
TLC/mm^3	Mean	9601.25	8566.29	12614.4	19.0	<0.001**	0.103	0.0013*	<0.001**
	±SD	2423.83	1972.97	4307.87					
Neut./mm^3	Mean	7206.25	6131.48	10282	66.97	<0.001**	<0.001**	<0.001**	<0.001**
	±SD	2183.45	1630.29	4108.1					
Neut.%	Mean	74.2	70.97	79.08	21.88	<0.001**	0.054	<0.001**	<0.001**
	±SD	8.27	5.57	12.02					
Lymph./mm^3	Mean	1783.54	1961.85	1708.8	3.5	0.17	-	-	-
	±SD	607.28	500.1	674.18					
Lymph.%	Mean	19.29	23.21	15.8	26.42	<0.001**	0.0019*	0.0058*	<0.001**
	±SD	7.28	4.27	11.04					
NLR	Mean	4.55	3.2	6.94	59.73	<0.001**	0.006*	<0.001**	<0.001**
	±SD	2.55	0.87	3.47					
TP (gm/dl)	Mean	5.45	6.38	5.58	24.9	<0.001**	<0.001**	0.64	<0.001**
	±SD	0.82	0.55	0.55					
LDH (IU/L)	Mean	830.54	684.14	1380.5	30.32	<0.001**	0.035*	<0.001**	0.001**
	±SD	243.13	209.53	830.08					

MPE: malignant pleural effusion, TPE: tuberculous pleural effusion, PPE: para-pneumonic effusion, KW: Kruskal Wallis test, P1: p-value calculated by Tukey's post-Hoc test between malignant and tuberculous groups, P2: p-value calculated by Tukey's post-Hoc test between malignant and para-pneumonic groups, P3: p-value calculated by Tukey's post-Hoc test between tuberculous and para-pneumonic groups, SD: standard deviation, *: statistically significant, **: statistically highly significant, TLC: total leucocytic count, Neut.: neutrophils, Lymph.: lymphocytes, mm3: cubic milliliter, NLR: neutrophil to lymphocyte ratio, TP: total protein, LDH: lactate dehydrogenase, -: Tukey's post-Hoc test could not be applied due to non-significant p-value calculated by Kruskal Wallis test.

Table (5): Peripheral blood parameters distribution among studied groups

The mean peripheral blood TLC was significantly higher among the patients of (PPE) group compared with (MPE) and (TPE) groups (p= 0.0013 and <0.001) respectively. The mean neutrophils count and percentage in peripheral blood were greatly higher in (PPE) group compared with the other groups (p <0.001). Furthermore, the same count

was higher in (MPE) group versus (TPE) group (p <0.001), but the percentage was not significantly differ (p= 0.054). The mean hematological lymphocytes percentage was significantly higher in (TPE) group compared with (MPE) and (PPE) groups (p= 0.0019 and <0.001) respectively. Moreover, the previos percentage was also higher in (MPE) group compared with (PPE) group (p= 0.0058). However, the mean lymphocytes count in peripheral blood did not differ significantly among the study groups (p= 0.17). The mean hematological (NLR) was significantly lower in (TPE) group compared with other groups (p <0.001). As well, this ratio was significantly lower in (MPE) group versus (PPE) group (p= 0.006). The mean (NLR) in peripheral blood was (3.2±0.87) in (TPE) group, (4.55±2.55) in (MPE) group and (6.94±3.47) in (PPE) group. (Table 5).

DISCUSSION

In our study, we intended to investigate (NLR) as an easily-calculated biomarker, which may take a role in distinguishing common causes of exudative pleural effusion.

We observed significant increases in the mean pleural fluid TLC , as well as neutrophils count and percentage among the patients of (PPE) group compared with other groups. The mean pleural fluid neutrophils count and percentage were significantly lower in (TPE) group compared with (MPE) group also. On the other side, the mean lymphocytes percentage in pleural fluid was significantly higher in (TPE) group compared with others, and a similar significant difference was discovered between (MPE) and (PPE) groups. At the same time, the mean lymphocytes count in pleural fluid did not differ significantly among the study groups.

These findings agree with those of a leading study, included 140 patients underwent thoracentesis for diagnostic purposes, and revealed that the elevated percentage of lymphocyte in tuberculous effusions can distinguish it from parap-neumonic effusions (p <0.001), nonspecific effusions (p <0.001), effusions caused by indefinite connective tissue disorders (p <0.001) and rheumatoid effusions (p= 0.005). Although, the former study concluded that a major lymphocytic prevalence is a particular characteristic for tuberculous effusions, it disclosed that the same condition may occur with malignant pleural effusions, so that this prevalence cannot be marked as a disease-discriminating finding.[12]

The most common etiologies of lymphocytic effusions are tuberculosis (TB), malignancy and congestive heart failure. Other causes include lymphoma, post-cardiac bypass graft, renal or liver failure, rheumatoid arthritis and rarely parapneumonic effusions (PPE) .[13]

A neutrophil proportion of more than one half of pleural fluid TLC is commonly seen with PPEs. Despite that, about 10% of tuberculous effusions can also be neutrophilic-predominant.[14]

The predominant WBC population in pleural fluid is defined by the mechanism of pleural injury. Thus, effusions rich in neutrophils raise the possibility of pleural infection (an acute process), whereas effusions with abundant lymphocytes enhance the diagnosis of cancer or tuberculosis (a chronic process) [15]. Moreover, lymphocytic predominance in (TPE) observed in the work was reported by other studied.[16, 17]

In the current study, the mean pleural fluid TP was significantly higher in (TPE) group compared with (MPE) and (PPE) groups, while the mean pleural fluid LDH was significantly elevated in (PPE) group versus (TPE) and (MPE) groups. On the other hand, the mean serum TP was significantly higher in (TPE) group compared with other groups. The mean serum LDH was significantly elevated in (PPE) group versus other groups. As well, the mean serum LDH was significantly elevated in (MPE) group compared with (TPE) group.

These observations completely correspond to those of Samanta et al.[18] who found that the mean serum TP was significantly higher in TB group (6.865± 0.399 g/dl) than lung cancer group (5.304 ± 0.383 g/dl) (p <0.0001). Furthermore, the mean pleural fluid TP was significantly higher in TB group (4.94± 0.2 g/dl) compared with lung cancer group (3.904±0.416 g/dl) (p <0.0001). In addition, the mean serum LDH was higher in cancer group (921.46 IU/L) than in TB group (468.41 IU/L) (p <0.0001).[18]

They also merge with a Chinese study included 72 patients with (TPE) and 47 patients with (PPE) which recorded (364.5 IU/L and 4037 IU/L) as the median pleural fluid LDH in (TPE) and (PPE) groups respectively (p < 0.0001).[19]

Apart from our findings, Lee et al., deduced that high pleural fluid LDH may be detected in pleural effusions due to different causes. They also documented that pleural fluid LDH tend to range from normal to extremely increased levels, which limits its chance for distinguishing (PPE) patients due to its low sensitivity.[20]

This study revealed that the mean pleural fluid (NLR) was significantly different among the three groups (p <0.001), being lowest in (TPE) group, intermediate in (MPE) group and highest in (PPE) group. These findings are matching with those of a large Turkish study (465 patients), which showed that the mean pleural fluid (NLR) value was significantly lower in tuberculous pleural effusion compared with malignant, para-pneumonic and para-malignant effusions (p <0.001, <0.001 and 0.012) respectively [1]. However, in the later study the mean pleural fluid (NLR) did not significantly differ between malignant and para-pneumonic groups. This could be attributed to the majority (83.33%) of malignant mesothelioma cases in our (MPE) group, which is known by its lymphocytic-rich exudative pleural effusion.

Furthermore, the abundance of malignant mesothelioma patients in our study, which is known by its short life expectancy (12-21 months), with a median overall survival of about 15 months, rendering it one of the worst tumors as regard prognosis [21], makes our results parallel to those of a recent study with 117 (MPE) patients which exposed that NLR (>0.745) in malignant pleural fluid was indicative to unfavorable prognosis.[22]

Finally, in our work we found that the mean hematological (NLR) was significantly lower in (TPE) group compared with other groups. At the same time, this ratio was significantly lower in (MPE) group versus (PPE) group. These perceptions are convenient with those of Arghir et al.[23] who investigated 463 patients (110 MPEs and 353 TPEs), and demonstrated that the mean hematological (NLR) was significantly lower in (TPE) patients (4.40±9.75) compared with (MPE) patients (4.94±4.19) (p <0.001). They also concluded that hematological (NLR) seems to be useful in the separation between malignant and TB pleural effusions. [23]

Limitations

Unequal distribution of patients among the study groups, in addition to lack of presentation of many malignant pathologies within (MPE) group and the confinement on most common causes of exudative pleural effusion only are the main limitations existed in our study.

CONCLUSION

Neutrophil to lymphocyte ratio in either blood or pleural fluid is an easily-obtained and cost-effective biomarker which can differentiate between (MPE), (TPE) and (PPE). Further studies with larger sample sizes and more varieties of malignant patients are required to confirm our results.

Conflict of interest : none

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