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Review

Etiology of exudative pleural effusion among adults: differentiating between tuberculous and other causes, a multicenter prospective cohort study

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ABSTRACT

Objectives: Exudative pleural effusions have a broad etiology and usually necessitate further investigative workup, including invasive procedures. This study aimed to evaluate and compare the demographic, clinical, and biochemical characteristics of tuberculous, malignant, and chronic inflammatory pleural effusions.
Methods: This is a 2-year prospective cohort study of patients referred for medical thoracoscopy with an exudative pleural effusion.
Results: A total of 159 patients were enrolled in the study, with a mean age of 42.49 ± 13.8 years and the majority being males 121 (76.1%). As expected, patients with tuberculous effusions were significantly younger than those with non-tuberculous effusions (37.7 ± 10.9 vs 49.1 ± 14.9, P <0.001). Serum analysis showed significantly lower white blood cell count (7.5×10^9/L ± 2.7 vs 9.0×10^9/L ± 3.3, $P = 0.004$), higher total protein (76.2 g/dL ± 10.1 vs 70.2 g/dL ± 8.9, P <0.001), and higher median C-reactive protein (median 77.5, interquartile range 51-116 vs median 40.5, interquartile range 8-127, P <0.001) among tuberculous compared with non-tuberculosis effusions.
Conclusions: Our study validates previous findings showing similar results in patients with tuberculous pleural effusions. A predictive model incorporating different demographic and clinical/laboratory characteristics may be useful in the early etiologic characterization of exudative pleural effusion.

Introduction

Pleural effusion builds up from an imbalance between hydrostatic pressure and oncotic pressure in the capillaries, pleural space, and the lymphatic system [1] and can be classified as either transudative or exudative based on chemical contents, as per Light's criteria [2]. A wide spectrum of etiologies can lead to pleural effusion, depending on the geographic region and local demographics. In high-resource countries, the common causes of pleural effusions in adults are cardiac failure, malignancy, and pneumonia [3], whereas in low-resource countries, tuberculosis (TB) and parapneumonic effusions are more prevalent [4]. A local study done in Qatar concluded that TB is the most frequent cause of pleural effusion (32.5%), followed by pneumonia (19%), cancer (15.5%), and cardiac failure (13%) [5].

A preliminary diagnosis is usually made in most patients based on clinical features and pleural fluid analysis. However, definitive diagnosis of exudative effusion is usually made by either identification of malignant cells, specific organism in pleural fluid, or histologic findings in pleural biopsy [6]. Pleural biopsy can be obtained via closed needle biopsy, medical thoracoscopy, or video-assisted thoracic surgery. Thoracoscopy is a highly sensitive tool for the evaluation of undiagnosed exudative pleural effusions; however, it is an invasive procedure with its own complications [7].

Therefore, we designed this study to identify the most common causes of exudative pleural effusion cases in Qatar and compare the

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clinical and biochemical characteristics of these cases, with the hope to reach a scoring model in the future that can be used with high accuracy to diagnose the cause of exudative pleural effusions without the need for more invasive interventions such as pleural biopsy.

Study design

This is a 2-year prospective cohort study that included patients admitted with an exudative pleural effusion in multiple centers under the umbrella of Hamad Medical Corporation between September 2020 and August 2022.

Inclusion and exclusion criteria

The inclusion criteria included all adult patients aged ≥14 years with an exudative pleural effusion admitted to the centers enrolled in the study, with pleural effusion >1 cm on a decubitus chest X-ray or >200 mL on posteroanterior chest X-ray.

The exclusion criteria included transudative pleural effusion and patients with recurrent pleural effusion.

Study methodology

Patients that fit the inclusion criteria from Hamad General Hospital, Alkhor Hospital, Alwakra Hospital, and Hazem Mberik General Hospital were recruited in the study. The demographic and clinical data collected included age, sex, nationality, smoking status, chief complaints, previous cancer diagnosis, comorbidities, duration of symptoms, vital signs, and types of interventions. Pleural fluid analysis data included white blood cells (WBCs), red blood cells, protein, lactate dehydrogenase (LDH), glucose, pH, Gram stain and culture, acid fast bacilli stain and culture, TB polymerase chain reaction, and cytopathology. For this study, we also collected pleural fluid samples for the measurement of adenosine deaminase (ADA). All routine blood test results on WBC, C-reactive protein (CRP), procalcitonin, lactic acid, glucose, LDH, and protein were noted. The patients underwent confirmatory diagnostic tests based on hospital guidelines for the evaluation of exudative pleural effusion that involves thoracoscopy and pleural biopsy if the initial thoracentesis was non-diagnostic.

Ethical considerations

This study was approved by the medical research center and institutional review board of Hamad Medical Corporation, Doha, Qatar (MRC -01-19-359). All patient data were anonymous, and personal identifiers were excluded from data collection forms. Consent forms have been obtained from all participants by the treating medical team.

Statistical consideration and data analysis

Descriptive statistics were used to summarize and describe the sample characteristics and distribution of the participants' data. Normally distributed data and results are presented as mean and SDs, whereas skewed or non-normal data are presented with medians, along with interquartile ranges (IQRs). Categorical data were summarized using frequencies and percentages. Associations between two or more qualitative data variables were assessed using the chi-square (χ^2) test or yates corrected chi-square test, as appropriate. Quantitative data and outcomes (age, serum, and pleura fluid analysis–related parameters) between the two (TB vs non-TB pleural effusion) and more than two independent groups (tuberculous pleural effusion [TPE], chronic inflammatory pleural effusion [CPE], and malignant pleural effusion [MPE]) were analyzed using unpaired *t* test and one-way analysis of variance statistical method. The corresponding non-parametric Mann–Whitney *U* test and Kruskal–Wallis test were applied for non-normal data distribution. Box plots were constructed to depict the distribution of ADA, serum, and pleura fluid analysis–related parameters across TB and non-TB pleural effusions. All statistical *P*-values presented were two-tailed, and $P < 0.05$ were considered statistically significant. All statistical analyses were performed using the SPSS Version 29.0 (IBM Corp., Armok, NY, USA) and Epi-info (Centers for Disease Control and Prevention, Atlanta, GA) software.

Results

A total of 159 patients were enrolled in the study (Table 1). Among the study participants, 121 (76.1%) were male, with a male-to-female ratio of 3:1. The age of participants ranged from 14 to 80 years, with a mean 42.49 ± 13.8 years. Most patients (145 [92.2%]) were expatriates. A history of diagnosis of malignancy was noted in only 16 (10.1%) patients. Smoking was a possible potential risk factor that was noted in only 46 (28.9%) patients. The most common presenting symptoms were dyspnea (50.3%), followed by chest pain (47.2%), fever (47.2%), weight loss (34%), and cough (30.8%). Most of the study population (50%) had a duration of 1-4 weeks of symptoms before coming to the hospital.

The serum biochemical tests (Table 2) showed that the overall mean WBC count was 8.2 ± 3 × 10^9/L, with an elevated CRP (median 66, IQR 33.3-115.8 mg/dL) and mean LDH 227.4 ± 72.1 IU/L. The pleural fluid laboratory results showed leukocytosis with a median WBC of 2281 (IQR 1224.5-4906.3 × 10^9/L), with 68.8% lymphocytes and mean LDH of 456.6 ± 305.5 IU/L, and elevated protein level 51.3 ± 10.6 mg/dL. The range of pleural fluid ADA was 54.4 ± 33.3 U/L (IQR 25-81.6).

Pleural biopsy was conducted for diagnostic purposes in 112 (70.4%) patients: medical thoracoscopy with pleural biopsy was done in 94 (84%) and video-assisted thoracic surgery pleural biopsy in 18 (16%) patients. The most frequent etiology of exudative pleural effusion was TPE in 58.5% of patients, followed by CPE (26.4%) and MPE (15.1%). Tables 3 and 4 show the detailed distribution of the demographics, clinical characteristics, biochemical features, and diagnostic interventions across the three main diagnoses. Box plots depict the distribution of ADA, serum, and pleura fluid analysis–related parameters across TB and non-TB pleural effusions (Figure 1). MPE (28.6% vs 13.8%) and CPE (57.1% vs 23.4%) were found to be significantly higher, whereas

Table 1
Baseline characteristics of the study participants.

Parameters	Exudative pleural effusion (N = 159)
Age (mean± SD), years	42.49 ± 13.8
Gender	
Male	121 (76.1%)
Female	38 (23.9%)
Nationality	
Qatari	14(8.8%)
Non-Qatari	145(92.2%)
Smoker (current or previous)	46(28.9%)
Comorbidities	
Multiple comorbidities	46 (28.9%)
Malignancy	16 (10.1%)
Duration of symptoms[a]	
Less than 7 days	33 (20.3%)
7- 30 days	80 (50.6%)
More than 30 days	45 (28.5%)
Presenting symptoms	
Chest pain	75 (47.2%)
Cough	49 (30.8%)
Shortness of breath	80 (50.3%)
Fever	75 (47.2%)
Weight loss	54 (34%)
Hemoptysis	36 (22.6%)
Night sweats	27 (17%)

[a] The sum here is equal to 158 due to missing data and the respective percentage was computed on non-missing data. The duration of symptoms calculated based on the symptom that has the maximum duration.

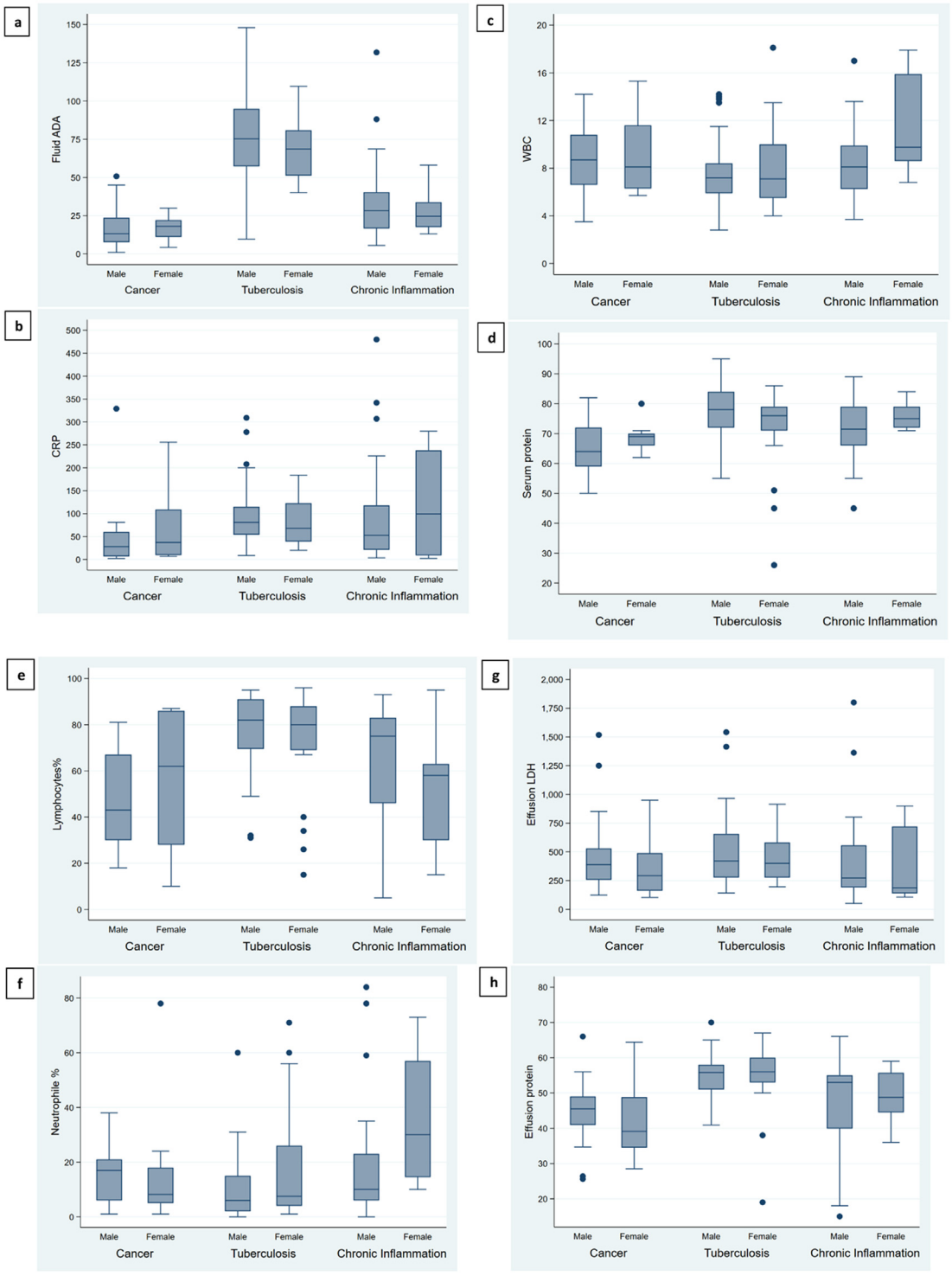

Figure 1. Box plots depicts the distribution of (a) fluid ADA, (b) CRP, (c) WBC, (d) serum protein, (e) lymphocytes %, (f) neutrophil %, (g) effusion LDH, and (h) effusion protein across the three diagnosis categories.
ADA, adenosine deaminase; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell.

Table 2
Biochemical results of serum and pleural fluid analysis.

Parameters		Exudative pleural effusion (N = 159)	
Serum analysis	n	Mean ± SD	Median (interquartile range)
White blood cells (× 10^9/l)	159	8.16 ± 3.01	7.8 (6.10,9.50)
C-reactive protein (mg/dl)	156	87 ± 77.3	66 (33.25,115.75)
Procalcitonin (mg/dl)	70	5.68 ± 38	0.11 (0.06,0.30)
Lactic acid (mg/dl)	100	1.44 ± 0.80	1.30 (1.00,1.68)
Glucose (mmol/l)	149	6.6 ± 5.75	5.8 (5.20,6.75)
Lactate dehydrogenase (IU/l)	92	227.36 ± 72.09	210 (180,263.75)
Protein (mg/dl)	158	73.69 ±10.03	74.5 (69.00,81.00)
Pleural fluid analysis			
White blood cells (× 10^9/l)	150	3811.23 ± 4784.30	2281 (1224.50,4906.25)
Lymphocytes (%)	148	68.86 ± 23.22	76 (58.00,86.75)
Neutrophil (%)	143	14.88 ± 18	9 (3.00,20.00)
Lactate dehydrogenase (IU/l)	148	456.59 ± 305.49	391 (228.25,592.50)
Protein (mg/dl)	148	51.31 ± 10.55	53.4 (46.25,58.00)
Glucose (mmol/l)	147	5.53 ± 2.82	5.20 (4.20,6.40)
Adenosine deaminase (U/l)	159	54.4 ± 33.26	51.23 (25.04,81.57)

Table 3
Differentiating features of clinical parameters and interventions between tuberculous pleural effusion, malignant pleural effusion, and chronic inflammatory cause of pleural effusion.

Parameter	Cancer N = 24 (15.09%)	Tuberculosis N = 93 (58.49%)	Chronic inflammation N = 42 (26.42%)	*P*-value
Age (years) (mean ± SD)	53.88 ±13.26	37.78 ±10.91	46.4 ± 15.27	<0.001
Gender				
Male	15 (62.5%)	70 (75.3%)	36 (85.7%)	0.100
Female	9 (37.5%)	23 (24.7%)	6 (14.3%)	
Nationality, % (Qatari/Non-Qatari)	(28.6 / 71.4)	(14.3 / 85.7)	(57.1 / 42.9)	**<0.001**
Smoker (current or previous)	7 (29.16 %)	24 (25.8 %)	15 (35.71 %)	0.588
Previous diagnosis of malignancy	11 (45.8 %)	1(1.07 %)	4(9.52 %)s	**<0.001**
Presence of multiple comorbidities	5 (20.8 %)	8 (8.60 %)	12 (28.5 %)	**0.002**
Duration of symptoms:				**0.010**
Less than 7 days	4 (16.6%)	20 (21.5%)	8 (19%)	
7-30 days	6 (25%)	55 (59.1%)	19 (45.2%)	
More than 30 days	14 (58.3%)	17 (18.3%)	14 (33.3%)	
Presenting symptoms				
Chest pain	10 (41.6%)	41 (44%)	24 (57.1%)	0.267
Cough	8 (33.3%)	30 (32.2%)	11 (26.2%)	0.768
SOB (Shortness of Breath)	12 (50%)	51 (54.8%)	17 (40.5%)	0.328
Fever	5 (20.8%)	55 (59.1%)	15 (35.7%)	**0.001**
Weight loss	11 (45.8%)	35 (37.6%)	8 (19%)	**0.044**
Hemoptysis	3 (12.5%)	28 (30%)	5 (11.9%)	**0.030**
Types of intervention				
Thoracentesis	22 (91.6%)	82 (88.2%)	35 (83.3%)	0.653
Medical thoracoscopy	8 (33.3%)	67 (72%)	19 (45.2%)	<0.001
Video-assisted thoracoscopic surgery	2 (8.3%)	5 (5.38%)	11 (26.2%)	0.002

TPE (14.3% vs 62.8%) was noted significantly lower in non-Qataris, P <0.001. Patients with TPE was observed to be significantly younger age than those in with MPE and CPE (P <0.001). Patients with TPE had a subacute presentation, with 59.1% with a symptom duration of 7-30 days vs 58.3% of those with MPE having a symptom of more than 30 days, P = 0.010. Regarding the presenting symptoms, fever was significantly more frequent in those with TPE than in those with CPE or MPE (59.15% vs 35.7% vs 20.8%; P = 0.001), along with hemoptysis (30% vs 11.9% vs 12.55; P = 0.030). The mean WBC was found to be significantly lower in TPE than in CPE and MPE groups (P = 0.003), whereas the median CRP (P = 0.002) and protein (P <0.001) were observed to significantly higher in TPE than in the CPE and MPE groups. Although there were statistically insignificant differences in some of the parameters related to pleural fluid analysis between MPE, TPE, and CPE, the clinically relevant differences was noted in the pleural fluid protein, with a mean of 43.65 mg/dL vs 54.84 mg/dL vs 47.39 mg/dL, respectively, with a P <0.001 and mean pleural fluid ADA, 16.97 U/L vs 73.96 U/L vs 32.47 U/L, respectively, with a P = 0.001.

Discussion

In our prospective cohort study, TB continues to dominate the cause of exudative pleural effusion being investigated by medical thoracoscopy in the state of Qatar for more than a decade [5]. Most of our study population were non-Qatari (92.2%), mainly from the Indian subcontinent, which may be attributed to the population demographics of Qatar [8] with high Indian subcontinent expatriates and to TB being most common cause of exudative effusion in India [9]. In a similar study done by Adeoye et al. [10], the most common cause of pleural effusion was TB in 32.9% of patients, followed by malignancy (29.1%) and pneumonia (15%).

There are five clinically relevant features in TPE that stand out in our study compared with those with malignant effusion or effusion secondary to inflammatory etiologies. As expected, patients with tuberculous effusions were significantly younger than those with non-tuberculous effusions in higher TB burden areas [11]. This contrasts with high-resource countries, where TB effusion occurs mainly in the

Table 4
Differentiating features of biochemical parameters in serum and pleural fluid between tuberculous pleural effusion, malignant pleural effusion, and chronic inflammatory cause of pleural effusion.

Parameter	Cancer N = 24 (15.09%)	Tuberculosis N = 93 (58.49%)	Chronic inflammation N = 42 (26.42%)	*P*-value
Serum analysis				
White blood cell ($\times 10^9$/l)	9.19 ± 3.10	7.55 ± 2.70	8.90 ± 3.43	**0.003**
C-reactive protein (mg/dl)[a]	28 (8,64)	77.5 (51,116)	53.0 (21,127)	**0.002**
Procalcitonin (mg/dl)[a]	0.14 (0.04,0.7)	0.09 (0.06,0.14)	0.16 (0.05,0.63)	0.847
Lactic acid (mg/dl)	1.99 ± 1.36	1.44 ± 0.60)	1.12 ± 0.53	0.931
Glucose (mmol/l)	6.55 ± 2.31	6.80 ± 7.19	6.42 ± 2.95	0.692
Lactate dehydrogenase (IU/l)	257.1 ± 118.09	233.2 ± 61.42	193.5 ± 46.08	0.368
Protein (mg/dl)	67.17 ± 7.69	76.20 ± 10.09	71.93 ± 9.16	**<0.001**
Pleural fluid analysis				
White blood cell ($\times 10^9$/l)[a]	2044 (837.5,3800)	2425 (1501,4710)	2375 (814,8300)	0.523
Lymphocytes (%)	50.09 ± 24.85	76.55 ± 17.04	61.00 ± 26.93	**<0.001**
Neutrophil (%)[a]	11.5 (6,21)	6.0 (3,16)	10.5 (7,28.5)	**0.010**
Lactate dehydrogenase (IU/L)[a]	387.5 (227,514.5)	415 (276,610)	257 (172, 558)	**0.029**
Protein (mg/dl)	43.65 ± 11.04	54.84 ± 7.24	47.39 ± 13.15	**<0.001**
Glucose (mmol/l)	5.60 ± 3.28	5.41 ± 2.23	5.76 ± 3.72	0.550
Adenosine deaminase (U/l)[a]	14.04 (8.39,22.65)	72.59 (56.64,90.75)	26.32 (16.78,38.89)	**0.001**

[a] Median and interquartile range are presented due to non-normal/skewed data distribution and the respective statistical *P*-values were computed using the non-parametric Kruskal–Wallis test; otherwise, one-way analysis of variance was used to compute statistical *P*-value for which the data followed an approximately normal distribution.

older population with a mean age of 49 years [12]. The second feature is the gender disparity. Males predominate the gender in each diagnosis; however, males with TPE account for 44% of the total sample size. Men are twice more likely than women to be diagnosed with TB [13], attributed to genetic susceptibility and impact on immune response by sex hormones and behavioral characteristics of high-risk behaviors and occupations and increased social contacts [14].

The third clinical attribute is a relevant history of malignancy, which was reported in one case in TPE and present in almost half of malignant effusion cases, and this clinical variable has been used as a strong marker for malignancy in multiple reported studies [15]. The fourth important clinical feature is the duration of symptoms. TPE usually presents as an acute or subacute illness, symptoms are present for less than 1 week in 21% of patients and present for less than 1 month in 60%; on the other hand, almost 60% of malignant effusion cases have symptoms for more than 30 days; these findings are comparable to other studies [16,17]. The symptom duration is shorter in those patients with free-flowing effusions than those with loculated effusions, as noted by Lee et al. [18]. Patients presenting in acute phase or early stages of TPE will likely have a neutrophil predominant free-flowing effusions [13], whereas, in later stages, there is an increasing lymphocyte trend with decreasing mycobacterial burden [18]. The last highly significant, albeit less clinically relevant, differentiating feature is fever. Most patients with TB typically experience fever, an uncommon symptom in MPEs. Thus, we found that 60% of patients with TB were febrile compared with only 20% of patients with malignancies. Other studies report that only 15% of patients with TPE were afebrile [19], with fever resolving within 2 weeks of starting anti-TB treatment; this can be explained by the infectious nature of TB with higher inflammatory response in the body [20].

Regarding biochemical variables, mean serum WBC level was significantly lower in pleural TB (7.55×10^9/L) and chronic inflammatory effusion (8.9×10^9/L) than MPE (9.19×10^9/L). Although this finding is similar to other studies [21,22]; there is no clear explanation and not of clinical significance. Higher mean serum LDH was found in MPE (257.1 IU/L) than TPE (233.2 IU/L) and CPE (193.5 IU/L). Although there is no statistical significance for this variation, this can be explained by the shift of energy production in tumor cells to the glycolysis pathway, which is a quick way of adenosine triphosphate generation via the help of LDH, and this gives the tumor cells the characteristic of faster growth rate [23]. The level of serum CRP was higher in TPE and CPE than MPE, and this is in keeping with its property as an acute-phase reactant. In addition, CRP level has been studied before as a biomarker to discriminate malignant effusion but was not included in the final scoring model due to limited significance [24].

Within biochemical parameters, we would like to highlight two clinically relevant characteristics. The first parameter is the pleural fluid lymphocyte that can range from 0% to 100%. The mean pleural fluid lymphocyte in the study population was 68% and significantly different among TPE (76.5%), MPE (50%), and CPE (61%). Several other studies have described lymphocyte predominance in 60-90% of cases of TPE [21,25]. Only exceptionally in 6.7% cases can the pleural lymphocyte count of <50% may occur in TPE [26]. Thus, when 80% lymphocyte is chosen as the reference level, TPE is, by far, the most frequent cause of pleural lymphocytosis [27]. The proposed mechanism of lymphocytosis is the interaction between *Mycobacterium* TB and the human immune system causing hypersensitivity reaction to mycobacterial proteins in the pleura [28]. The second biochemical parameter is pleural fluid ADA. ADA is a marker of clusters of differentiation 4+ lymphocyte activation in the pleural fluid [29]. In our study, the mean ADA value for the cohort was 54.4 IU/L, with TPE having the highest mean of 73.96 IU/L and the lowest mean of 16.97 IU/L in MPE. In low-risk areas (prevalence of TB <125 per 100,000 population), an ADA <40 IU/L can effectively rule out TPE in 97-98% of patients. In moderate- to high-risk populations, similar to our study cohort, an ADA level of ≥35-40 IU/L can be used to diagnose TPE with 92% sensitivity and 90% specificity [30].

To the best of our knowledge, this study is the largest prospective study exploring the etiology and differentiating clinical and biochemical features in exudative pleural effusion in the state of Qatar. Our findings are similar to those reported in other regional countries, such as Saudi Arabia, Iran, and Lebanon, where tuberculous, parapneumonic, and malignant effusions are the most common etiologies [14,30].

Although the study we presented provides valuable insights into the clinical and biochemical characteristics of tuberculous and malignant/non-TPEs, there are some limitations that should be considered. The study included only patients referred for medical thoracoscopy, which may have introduced selection bias. The study was conducted in a specific geographical location (Qatar), and the findings may not be directly applicable to other populations with different prevalence of TB or other etiologies of pleural effusions. The sample size of 159 patients may be relatively small, potentially limiting the generalizability of the results. Larger sample sizes would enhance the statistical power and reliability of the study findings.

Conclusion

The relevant clinical parameters that could differentiate TPE from malignant effusion and chronic inflammatory etiologies are age, gender, history of malignancy, acute to subacute duration of symptoms, and the presence of fever. Furthermore, the two relevant biochemical parameters that could help in this differentiation are pleural fluid lymphocytosis and adenosine deaminase level. A predictive model using several of the collected parameters is being developed and may help in the early etiologic diagnosis of exudative pleural effusion.

Declarations of competing interest

The authors have no competing interests to declare.

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Author contributions

All authors participated in the conception and design, acquisition, analysis and interpretation of data, critical manuscript revision for significant intellectual content, final approval, and consensus.

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