Validation of a simple computed tomography scoring system to predict the malignant nature of pleural effusion

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Objective We aimed to validate a computed tomography (CT) scoring system and assess its sensitivity and specificity to predict the malignant nature of pleural effusion that is exudative and of undetermined origin.

Patients and methods This is a retrospective study that enrolled 123 patients who were referred for medical thoracoscopy in the Chest Department, Alexandria Main University Hospital, between 2013 and 2017 for diagnosing exudative pleural effusion of undetermined origin. CT scans were reviewed by a radiologist who was blinded to the final diagnosis. We applied a scoring system that was generated by Porcel *et al.* Scoring results were then evaluated using the final diagnosis of thoracoscopic pleural biopsies as the reference.

Results The CT score showed a sensitivity and a specificity of 70 and 66.7%, respectively, with an negative predictive value 83% and a positive predictive value 48%, and the area under the receiver operating characteristic curve was 0.745.using a cut-off value of at least 7.

Conclusion The CT scoring system could not predict the malignant nature of exudative effusion with great accuracy.

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Introduction

Pleural effusion has been known to be a clinical challenge as differentiating benign from malignant effusion is not an easy task [1–3]. Contrast computed tomography (CT) is an important step in the diagnostic pathway of undiagnosed exudative pleural effusions [4]. Nevertheless, the value of CT in differentiating between benign and malignant causes of pleural disease is undetermined [5]. Few studies have explored the value of CT in predicting the malignant nature of pleural effusions [6–8]. This study aimed to validate a CT scoring system and assess its sensitivity and specificity to predict the malignant nature of pleural effusion that is exudative and of undetermined origin.

Patients and methods

This is a retrospective study that enrolled 134 patients who were referred for medical thoracoscopy in the Chest Department, Alexandria Main University Hospital, between 2013 and 2017 for diagnosing exudative pleural effusion after failure to reach a definite diagnosis using noninvasive workup. Patients of both sexes were included, aged 18 years or older, and presenting with exudative undiagnosed pleural effusion either unilateral or bilateral. Patients unfit for medical thoracoscopy, patients suffering from pleural effusion with extensive loculations, patients weighing more than 120 kg, patients whose data were incomplete, and finally patients whose final diagnosis was inconclusive were excluded from our study and the final number of patients who fulfilled our inclusion criteria was 123 patients.

Demographics, clinical data, laboratory investigations, and radiology of all patients were reviewed as well as the final diagnosis on the basis of histopathological and microbiological examination results of pleural biopsies obtained using medical thoracoscopy. The initial workup included plain radiograph of the chest postero-anterior (PA) view, pleural tapping, and analysis of pleural fluid (chemical, bacteriological smears and cultures, and cytopathological examination). CT scans were reviewed by a radiologist who was blinded to the final diagnosis. We applied a scoring system that was generated by Porcel *et al.* [8] (score sum ranging from 0 to 20; Table 1). Scoring results were then evaluated using the final diagnosis of thoracoscopic pleural biopsies as the reference. The performance parameters of the CT scoring system were evaluated including sensitivity, specificity; positive predictive value (PPV), negative predictive value (NPV), and area under receiver operating characteristic curve.

Table 1 Computed tomography scan score for predicting the malignant etiology of pleural effusions

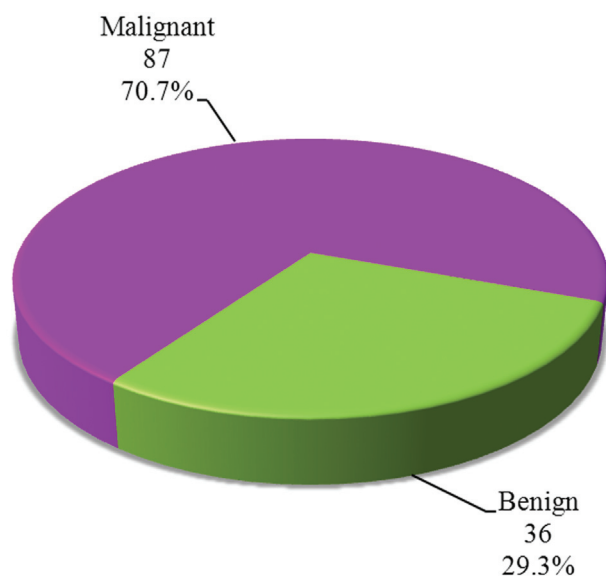| Parameters	Score
Any pleural lesion≥1 cm[a]	5
Liver metastases	3
Abdominal mass	3
Lung mass or lung nodule/s≥1 cm	3
Absence of pleural loculations	2
No pericardial effusion	2
Nonenlarged cardiac silhouette	2

[a]Any pleural lesion (i.e. nodule, mass, or thickening).

Statistical analysis of the data

Data were fed to the computer and analyzed using the IBM SPSS software package version 20.0. (IBM Corp., Armonk, New York, USA). Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, SD, and median. The significance of the results obtained was judged at the 5% level. The χ^2-test was used for categorical variables, to compare between different groups. Fisher's exact or Monte Carlo correction was used for correction for χ^2 when more than 20% of the cells have an expected count less than 5. The Student t-test for normally distributed quantitative variables was used to compare between two studied groups. The Mann–Whitney test was used for abnormally distributed quantitative variables to compare between two studied groups. A receiver operating characteristic curve (ROC) was generated by plotting sensitivity (TP) on the y-axis versus 1–specificity (FP) on the x-axis at different cut-off values. The area under the ROC curve denotes the diagnostic performance of the test. Area more than 50% yields acceptable performance and area about 100% is the best performance for the test. The ROC curve also allows a comparison of performance between two tests. Results were judged at a level of significance of 5%.

Results

We reviewed the data of 134 patients who underwent medical thoracoscopy during the period 2014 and 2018. We enrolled only 123 patients who fulfilled our inclusion criteria. The majority of the patients (70.7%) were finally diagnosed with malignant pleural effusion (Fig. 1). Demographic and clinical data of the patients studied are shown in Table 2. Patients with malignant disease were older than those with benign disease. Patients with malignant pleural effusion experienced cough, chest pain, and weight loss more significantly compared with patients with pleural effusion of benign nature. However, patients with benign pleural effusions suffered from fever more

Figure 1

Distribution of the studied cases according to the final diagnosis.

significantly than patients with malignant pleural effusion. The CT findings were compared between benign and malignant groups (Table 3). The presence of pleural thickening, pleural nodules, pleural masses, lung parenchymal nodules, or masses, in addition to isolated mediastinal pleural thickening, were significantly more common in the malignant group, whereas the presence of parenchymal consolidation was in favor of benign disease. The comparison between the CT score sum in the benign versus the malignant group is presented in Fig. 2. The performance of the CT score in predicting the malignant nature of the pleural effusion was assessed in terms of sensitivity, specificity, PPV, NPV, and area under the ROC curve (Table 4 and Fig. 3). The CT score showed a sensitivity and a specificity of 70 and 66.7%, respectively, with an NPV 83% and a PPV of 48%, and the area under the ROC curve was 0.745 and the 95% confidence interval was between 0.650 and 0.839 ($P<0.001$) using a cut-off value of at least 7. Use of higher cut-off values resulted in reduced sensitivity and higher specificity.

Discussion

Of 123 (71%) patients enrolled in this study, the majority of the patients were finally diagnosed with malignant effusion. We attribute this high prevalence of malignancy among our studied patients to the fact that the study was carried out in a tertiary care hospital; moreover, only patients who underwent medical thoracoscopy were enrolled, which might reflect indirect suspicion of malignancy from the clinician point of view in addition to the fact that 8% of our

Table 2 Comparison between the two groups studied according to demographic and clinical data

	Total (n=123) [N (%)]	Benign (n=36) [N (%)]	Malignant (n=87) [N (%)]	χ^2	P
Sex					
Male	59 (48.0)	22 (61.1)	37 (42.5)	3.523	0.061
Female	64 (52.0)	14 (38.9)	50 (57.5)		
Age (years)					
Minimum–maximum	20.0–86.0	20.0–81.0	26.0–86.0	t=2.965*	0.005*
Mean±SD	54.25±13.43	48.11±15.97	56.79±11.39		
Median	55.0	49.0	60.0		
Asbestos exposure					
No	113 (91.9)	33 (91.7)	80 (92.0)	0.003	FEP=1.000
Yes	10 (8.1)	3 (8.3)	7 (8.0)		
Smoking history					
No smoking	90 (73.2)	27 (75.0)	63 (72.4)	0.087	0.768
Ex or current smoker	33 (26.8)	9 (25.0)	24 (27.6)		
History of previous cancer					
No	102 (82.9)	33 (91.7)	69 (79.3)	2.746	0.098
Breast cancer	13 (10.6)	2 (5.6)	11 (12.6)	1.353	FEP=0.342
Bladder cancer	2 (1.6)	0	2 (2.3)	0.841	FEP=1.000
Other types	6 (4.9)	1 (2.8)	5 (5.7)	0.484	FEP=0.670
Complain					
Cough	55 (44.7)	11 (30.6)	44 (50.6)	4.128*	0.042*
Dyspnea	119 (96.7)	35 (97.2)	84 (96.6)	0.036	FEP=1.000
Pain	68 (55.3)	11 (30.6)	57 (65.5)	12.590*	<0.001*
Hemoptysis	2 (1.6)	0	2 (2.3)	0.841	FEP=1.000
Fever	12 (9.8)	7 (19.4)	5 (5.7)	5.426*	FEP=0.039*
Weight loss	60 (48.8)	11 (30.6)	49 (56.3)	6.766*	0.009*

*P≤0.05, statistically significant.

Table 3 Comparison between the two groups studied according to computed tomography findings

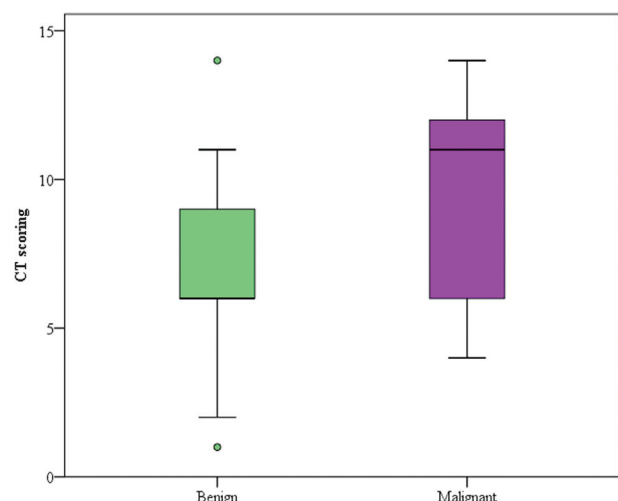| Computed tomography findings	Total (n=123) [N (%)]	Benign (n=36) [N (%)]	Malignant (n=87) [N (%)]	χ^2	P
Mediastinal lymph nodes	33 (26.8)	7 (19.4)	26 (29.9)	1.414	0.234
Pleural Nodules	32 (26.0)	0	32 (36.8)	17.898*	<0.001*
Pleural masses	16 (13.0)	1 (2.8)	15 (17.2)	4.707*	FEP=0.037*
Isolated mediastinal pleural affection	19 (15.4)	0	19 (21.8)	9.298*	0.002*
Circumferential affection	35 (28.5)	11 (30.6)	24 (27.6)	0.110	0.740
Pleural loculations	21 (17.1)	8 (22.2)	13 (14.9)	0.953	0.329
Pleural calcification	1 (0.8)	0	1 (1.1)	0.417	FEP=1.000
Pericardial effusion	4 (3.3)	1 (2.8)	3 (3.4)	0.036	FEP=1.000
Lung parenchyma					
Mass	15 (12.2)	1 (2.8)	14 (16.1)	4.215*	FEP=0.040*
Nodules	26 (21.1)	1 (2.8)	25 (28.7)	10.292*	0.001*
Consolidation	21 (17.1)	12 (33.3)	9 (10.3)	9.504*	0.002*
Pleural thickening>1 cm					
No	41 (33.3)	15 (41.7)	26 (29.9)	19.667*	<0.001*
Smooth	40 (32.5)	19 (52.8)	21 (24.1)		
Irregular	42 (34.1)	2 (5.6)	40 (46.0)		

*P≤0.05, statistically significant.

studied patients reported heavy occupational exposure to asbestos. Other studies showed a lower prevalence of malignancy of about 25% [1,9].

We compared benign and malignant patient groups in terms of the individual parameters used in the CT scoring system and other CT findings (Table 2). Some parameter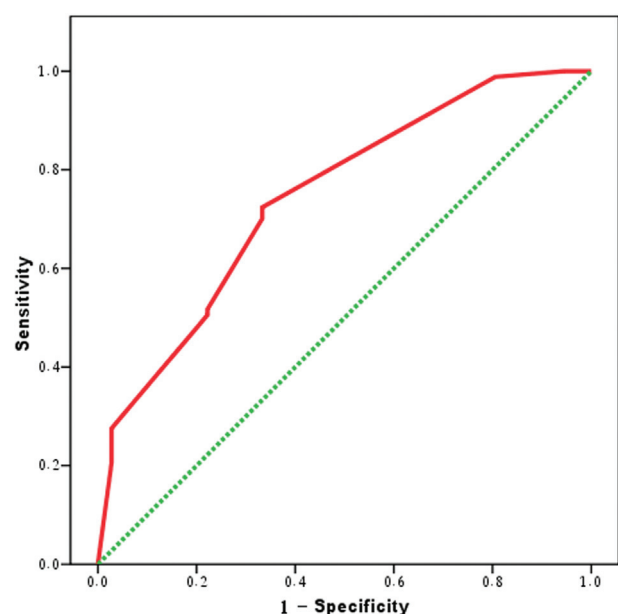s such as pleural thickening, pleural nodules, pleural masses, lung parenchymal nodules, and lung masses were seen significantly more frequently in the malignant group of patients in comparison with the benign group (P<0.05). However, other parameters of the cardiac silhouette did not show any significant difference between both groups. The presence of isolated mediastinal pleural lesion, although not included in this score, was significantly more

Figure 2

Comparison between the two groups studied according to computed tomography scoring.

Figure 3

Receiver operating characteristic curve for computed tomography scoring as a predictor for malignancy.

Table 4 Agreement (sensitivity, specificity, positive predictive value, and negative predictive value) for computed tomography scoring as a predictor for malignancy

Score cut-off	Sensitivity	Specificity	PPV	NPV
≥6	72.41	66.67	84.0	50.0
≥7	70.11	66.67	83.56	48.0
≥8	70.11	66.67	83.56	48.0
≥9	51.72	77.78	84.91	40.0
≥10	50.57	77.78	84.62	39.44

NPV, negative predictive value; PPV, positive predictive value.
*$P \leq 0.05$, statistically significant.

biopsies, yielding a sensitivity of 68% and a specificity of 78% [7].

The score that we used in this study was derived and validated by Porcel *et al.* [8] Their study reported that this CT score using a sum score of 7 or more as a cut-off value yielded a sensitivity of 88%, a specificity of 94% [95% confidence interval (CI): 83–98%], and an area under the receiver operating characteristics curve of 0.919 (95% CI: 0.849–0.990). In contrast, in our study, using this cut-off value, this score showed lower performance as the sensitivity and specificity were 70 and 66.7%, respectively, with an NPV of 83% and a PPV of 48%, and the area under the ROC curve was 0.745. It is worth noting that unlike Porcel *et al.* [8], who enrolled only patients with unilateral effusion, in this study, we enrolled patients with both unilateral and bilateral effusion.

The results of this study showed that a simple score on the basis of CT findings is not very accurate or reliable. Use of special techniques might improve the performance of a CT-based score. A recent study reported that pleural attenuation is more evident for the delayed phase in comparison with the early phase of contrast-enhanced CT chest [13]. Another study validated a simple PET-CT score and showed that it can be useful to differentiate malignant from benign causes of pleural disease [14]. In this study, five PET-CT parameters proved to be predictive of malignancy. These were unilateral lung nodules and/or masses with increased ^{18}F-FDG uptake; extrapulmonary malignancies; pleural thickening with increased 18Flourine-FluoroDeoxyGlucose (^{18}F-FDG) uptake; multiple nodules or masses in one or both lungs with increased ^{18}F-FDG uptake; and increased pleural effusion ^{18}F-FDG uptake. No single individual CT-PET parameter was predictive of malignancy, but was useful when combining more than one parameter together. A score of 4 or greater produced area under the curve, sensitivity, and specificity of 0.949, 83.3, and 92.2%, respectively, which is much higher than the AUC, sensitivity, and specificity in our study.

frequent in patients with malignant effusion. The addition of this parameter might improve the performance of this CT scoring system. A number of previous studies found that CT findings of pleural nodularity, thickening of mediastinal pleura, and thickening of parietal pleural more than 1 cm and circumferential pleural thickening could predict the malignant cause of pleural effusion, with specificities ranging from 90 to 100% and sensitivities of 40–60% [10–12]. Another study investigated the sensitivity and specificity of CT in detecting the malignant cause of pleural effusion according to the radiologist impression before pathology results of thoracoscopic pleural

However, a meta-analysis of 14 studies reported that PET imaging showed a significantly lower sensitivity for diagnosing malignant effusions than visual assessments (82 vs. 91%; P=0.026). Semiquantitative interpretations for identifying malignant effusions showed a sensitivity of 81%, a specificity of 74%, and area under the curve of 0.838, concluding that the moderate accuracy of the technique using 18-fluorodeoxyglucose is against its routine use to differentiate malignant from benign pleural effusions [15]. The same author developed and validated a CT scoring system for adults with parapneumonic pleural effusion that may allow clinicians to predict the need for chest tube drainage with good accuracy [16].

A large proportion of patients investigated for suspected malignant disease will show final results of malignancy irrespective of CT report impression; hence, the CT solely should not direct whether patients with pleural effusion should undergo further invasive pleural biopsies or not. This is in agreement with a retrospective series that suggests that approximately one-third of the patients with pleural malignancy may not show evident features of cancer on CT [17]. Moreover, in the study of Safwat et al. [18], although a sensitivity of 70% was found for CT chest to detect primary pleural tumors as 'high', CT chest failed to define parietal pleural invasion in 30%, visceral pleural involvement in 60%, and fibrinous septations in 10% of their enrolled patients.

Whether CT could save fragile patients, a more invasive procedure was an important consideration, if combined with close follow-up and observation. Adding mediastinal pleural lesion to CT parameters may improve the performance of this score in addition to considering other factors such as patient age, which was significantly higher in the malignant group of patients; in addition, important clinical data such as cough, chest pain, and significant weight loss were significantly more frequently reported also by the malignant group of patients, whereas the presence of fever was in favor of benign rather than malignant effusion.

In our opinion, creating a score that combines CT parameters with age and clinical data may be more informative and predictive of the final patient diagnosis than an isolated score based merely on CT. All the studies that discussed CT scores as predictors of malignancy showed low sensitivity even if the specificity was high. This is not accepted in a disease such as pleural effusion that is known that the majority of its patients will eventually turn out

to be malignant. The strengths of our study were the fact that thoracoscopic pleural biopsy was considered the reference standard for the final diagnosis as well as the relatively large number of patients studied. The limitations of the current study are as follows: patients who were unfit or refused medical thoracoscopy were not included. Patients with extensive adhesions were also excluded as this was a contraindication for medical thoracoscopy. Morbidly obese patients whose weight exceeded that allowed to lay supine on CT table were also excluded ($>120\,kg$). Furthermore, we only considered exudative pleural effusions, whereas malignancy can be associated with transudative effusion [19–21].

Conclusion

CT-based scoring system cannot predict the malignant nature of exudative effusion with high accuracy; neither can it help taking the decision to continue or stop further investigations.

Conflicts of interest
There are no conflicts of interest.

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