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CT Assessment of Subtypes of Pulmonary Emphysema in Mongolian Miners

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Objectives: To determine the incidence of subtypes of pulmonary emphysema identified by LDCT imaging and the relationship between emphysema subtypes with smoking and pulmonary function in miners. **Methods:** We reviewed 329 miners (245 men and 84 women). Each miner had a low dose (LD) chest CT. Among them 75 miners had a standard chest CT. The images were reconstructed using contemporary iterative reconstruction. Lung volumes and emphysema severity was calculated using automated densitometry segmentation software and qualitative visual analyses.There were two subtypes of pulmonary emphysema found: centrilobular emphysema (CLE) and paraseptal emphysema (PSE). Based on these subtypes, CLE was divided into the following five categories: trace, mild, moderate, confluent, and advanced CLE. PSE was divided into the following two catergories: mild and substantial PSE. **Results:** Pulmonary emphysema was found in 89 (27.1%) of 329 miners. According to the survey, 73 (82.0%) miners had centrilobulor emphysema, and 17 (18.0%) had a paraseptal emphysema. The emphysema group was a lower Gensler index than thenon-emphysema group. The smoker group had higher emphysematous changes than the non-smoker groups ($p < 0.05$). **Conclusions:** Dose reduced CT isauseful study for the assessment of emphysema.

Keywords: Computed Tomography, Pulmonary Disease, Pulmonary Emphysema

Introduction

Computed tomography (CT) is a well-validated technique to visually and quantitatively assess the in vivo presence, pattern, and extent of emphysema [1-5]. Generally, pulmonary emphysema is classified into three types related to the lobular anatomy: centrilobular emphysema, panlobular emphysema, and paraseptal emphysema. At CT, CLE centrilobular emphysema is characterized by small well-defined or poorly defined areas of low attenuation surrounded by normal lung. Centrilobular pulmonary arteries or arterioles, which are often seen traversing the hypoattenuated areas, mark the center of each lobule and paraseptal emphysema refers to emphysematous change adjacent to a pleural surface [4, 6]. Centrilobular emphysema is the most common type of smoking-related emphysema and is usually upper lung predominant [7, 8]. The low-attenuation areas may range from less than 1 mm to more than 3 cm in diameter. PLE panlobular emphysema specifically refers to diffuse emphysematous destruction across the lobule and it was subsequently linked to low circulating levels or absence of α1-antitrypsin [9-11].

Paraseptal emphysema, also known as distal acinar emphysema, is characterized by the predominant involvement of the distal alveoli including their ducts and sacs, bounded by any pleural surface and the interlobular septa [12].

Quantitative and qualitative studies have shown that CT can allow distinguishing not only between airway and parenchymal abnormalities, but also between subtypes of emphysema [13-16]. Several studies have demonstrated association between quantitative measures of emphysema severity and physiologic parameters of lung function [17-20]. We hypothesized that pulmonary emphysema is more prevalanced in miners with dusty exposure. In Mongolia, subtype of emphysema has not been identified by CT, so we have evaluated the prevalence of emphysema in miners using low dose chest CT.

Hence the aim of this study was to evaluate subtypes of emphysema by low dose computer tomography and to determine therelationship between emphysema subtypes with pulmonary function in Mongolian miners.

Materials and Methods

Study population

We performed a cross-sectional, prospective study on329 miners with dust exposure. All participants were followed at the Medipas Hospital, Orkhon province, Mongolia, between April 2016 and May 2018 and were considered for participation in the study. Exclusion criteria were patients with tuberculosis, lung cancer, patients with a history of acute myocardial infarction, unstable angina or congestive heart failure and previous lung resection surgery.

Initially, we performed an evaluation of symptoms, tobacco use, and physical examination.Alung functional test was carried out before and 15 minutes after inhalation of 300 mg of salbutamol using a spirometer (CHESTGRAPH HI-105, Japan), and the values of force vital capacity (FVC), FEV1 and FEV1/FVC ratio were analyzed. The test was performed according to the ATS guidelines, and reference values for Caucasians were used. FVC and FEV1 were expressed as percent of the predicted value. Participants performed the 6 Minute Walking Test (MWT) under supervision of the same technician. The distance was measured in meters.

Imaging and imaging analysis

The chest HRCT scans were performed by using a 128-channel multidetector CT scanner (Sceneria, Hitachi, Japan) with reconstructions 1 mm thick. The scans were performed in the supine position with the breath held at full inspiration as well as in maximal expiration. The imaging parameters were 100-120 kV and 20-60 mAs (Low dose CT protocol). All low dose computer tomography (LDCT) images were independently reviewed by two radiologists. Their findings were individually recorded and the consensus findings were documented. Emphysema was classified morphologically using low dose CT into the following 3 subtypes in accordance with centrilobular, paraseptal, and panlobular emphysema types.

Visual emphysema subtype assessment

Two radiologists visually scored emphysema subtypes and airway disease on lung windows according to the Fleischner Society criteria. Briefly, emphysema subtypes were classified as centrilobular emphysema (CLE) and paraseptal emphysema (PSE).

CLE were classified into 5 subtypes, trace (occupying < 0.5% of a lung zone), mild (0.5-5% of a lung zone), moderate (more than 5% of any lung zone), confluent (coalescent centrilobular or lobular lucencies, but not involving extensive hyper expansion of secondary pulmonary lobules or distortion of pulmonary architecture) and advanced destructive (panlobular lucencies, with hyperexpansion of secondary pulmonary lobules and distortion of pulmonary architecture) emphysemas. Paraseptal emphysema was classified as mild (≤ 1 cm) and substantial (> 1 cm) emphysema [13]. Definitions of emphysema are depicted below.

Centrilobular emphysema

Focal regions of low attenuation surrounded by normal lung attenuationlocated within the central portion of secondary pulmonary lobules. As severity increases, vessels appear "pruned" and low attenuation regions enlarge.

Panlobular emphysema

Panlobular emphysema is characterized as diffuse regions of low attenuation involving entire secondary pulmonary lobules. As severity increases, paucity of peripheral vessels increases.

Paraseptal emphysema

Paraseptal emphysema has regions of low attenuation adjacent to visceral pleura (including fissures) [6, 12, 21, 22]. Interobserver agreement was categorized as slight, fair, moderate, good, or excellent based on κ values of 0.20 or less, 0.21–0.40, 0.41–0.60, 0.61–0.80, and 0.81 or higher, respectively.

Lung density assessment

Attenuation was assessed using standard reconstruction CT images with workstation (CT lung density software program, Intelli Space Portal, Philips Extended BrillianceTM Workspace V4.5.5.51035) (DELL PRECISSION T5500). Percent of emphysema like lung was defined as the percentage of total voxels within the lungfield below 950 Hounsfield units (percent emphysema<-950HU) [23].

Statistical analysis

When the data for the continuous variables showed a normal distribution, they were compared by T-test and Kruskal-Wallis H test. Pairwise comparisons were performed. Significant values have been adjusted by the Bonferroni correction for multiple comparison tests. Chi-square or Fisher exact test for independence to determine whether there isa significant relationship between two categorical variables. P-value of less than 0.05 was considered significant for the results of all statistical analyses. Data were analyzed by STATA 12 program.

Ethical statement

The study was approved by the Research Ethics Committee of the board of Mongolian National University of Medical Sciences (№2017/3-07). All patients signed their informed consent forms before participating in the study.

Results

A total of 245 miners (74.4%) males and 84 (25.6%) females) with a mean dust exposure duration 17.7 ± 5.0 years were recruited in this study. Table 1 shows the characteristics of the study population, including non-emphysema and emphysema groups. Compared with the non-emphysema group, the dust exposure duration was significantly longer in the emphysema group ($p < 0.02$). Moreover, the 6 MWT was shorter in the emphysema group with a value of 215.6 ± 53.3 ($p < 0.000$). Regarding the gender differences, the prevalence of emphysema was higher in both men and women.The result of this study also showed that, in non-smoking miners, emphysema was significantly lower than that in current smokers (15 vs 61), which in turn revealed an additive effect of smoking on emphysema.

Table 1. General characteristics of miners

Variables	Non-emphysema (n = 240)	Emphysema (n = 89)	p-value
	Mean ± SD	Mean ± SD	
Age (year)b	56.6 ± 8.5	59.4 ± 9.5	0.012*
Dust exposure (year)a,b	17.3 ± 4.8	18.8 ± 5.2	0.020*
BMIb	29.4 ± 5.0	25.8 ± 4.5	0.000
6MWTb	263 ± 87.4	215.6 ± 53.3	0.000*
mMRC Dyspnea scaleb	2.1 ± 1.5	2.2 ± 1.1	0.309
Gender a	N (%)	N (%)	
Male	164 (68.3)	81 (91.0)	0.000*
Female	76 (31.7)	8 (9.0)	0.000*
Age group			
5-14	56 (23.3)	16 (18.0)	0.509
15-24	141 (58.8)	57 (64.0)	
25-34	42 (17.5)	15 (16.9)	
35-44	1 (0.4)	1 (1.1)	
Smokinga			
Current smoker	97 (40.4)	61 (68.5)	0.000*
Former smoker	10 (4.2)	8 (9.0)	0.000*
Never	94 (39.2)	15 (16.9)	0.000*

[a]Mean value (Frequency (%)); [b]Mean value ± standard deviation; *< 0.05; BMI: Body mass index; 6MWT: Walking test in 6 minute; MMRC: Modified Medical Research Council

Table 2 shows subtypes emphysema and general characteristics of miners. It has been revealed that severity of CLE is significantly associated with reduced body mass index (p = 0.004). Moreover, compared with mild paraseptal emphysema (PCE), those with substantial PCE are significantly older and have lower BMI (24.6 ± 3.3 vs 27.0 ± 9.1). For LAA (percent of low attenuation areas), statistically significant association was found with emphysema severity (p = 0.000). There were statistically non-significant differences regarding dust exposure, oxygen saturation as well as tobacco usage on subtypes of emphysema.

Table 2. Subtypes emphysema and general characteristics

Variables	Trace (n = 12)	Low CLE (n = 31)	Medium CLE (n = 15)	Confluent CLE (n = 7)	Advanced CLE (n = 6)	Mild PCE (n = 9)	Substan-tial PCE (n = 5)	p-value
	I	II	III	IV	V	VI	VII	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age[a]	54.5 ± 8.2	59.3 ± 10.0*	61.8 ± 6.5	62.8 ± 12.6	67.2 ± 11.8	56.3 ± 9.4	69.8 ± 7.5*	0.005*
								II-VII 0.000
BMI[a]	27.9 ± 4.1	27.3 ± 4.2	25.6 ± 3.4*	23.4 ± 3.3	22.3 ± 2.6*	27.0 ± 9.1	24.6 ± 3.3	0.048*
								III-V 0.063
Dust[a]	16.3 ± 4.0	19.1 ± 5.1	18.4 ± 4.1	17.7 ± 6.1	22.5 ± 6.7	21.0 ± 6.9	19.0 ± 5.4	0.139
O2[a]	95.4 ± 1.5	94.7 ± 1.8	94.1 ± 2.1	92.8 ± 4.7	91.1 ± 5.7	95.5 ± 1.8	93.8 ± 3.9	0.498
FEV_1/FVC[a]	76.3 ± 9.4	75.8 ± 13.5	70.7 ± 8.4	60.8 ± 15.0	73.7 ± 21.6	72 ± 10.5	63.2 ± 9.8	0.191
Smoking[b]	8 (13.3)	17 (28.3)	13 (21.7)	4 (6.7)	6 (10.0)	8 (13.3)	4 (6.7)	0.084
LAA%[a]	8.8 ± 1.4	12.7 ± 1.5**	20.5 ± 3.9**	27.6 ± 1.9**	40.2 ± 4.8**	10.4 ± 0.8	21.9 ± 6.5	0.000*
								II-III 0.000
								II-IV 0.000
								II-V 0.000
								III-V 0.001

[a]Mean value ± standard deviation; [b]Mean value (Frequence (%)); * < 0.05; **< 0.000(Kruskal-Wallis); BMI: Body mass index;SLE: Centrilobular emphysema; PCE: Paraseptal emphysema; O_2: Oxygen saturation; LAA%: percent low attenuation areas

As seen in Figure 1, of the 329 participants, 89 miners (27.1%) had emphysema. Readers' agreement was good (k = 0.9). As to the severity of the emphysema, panlobular emphysema was not discovered, while mild and moderate centrilobular emphysema was more prevalent.

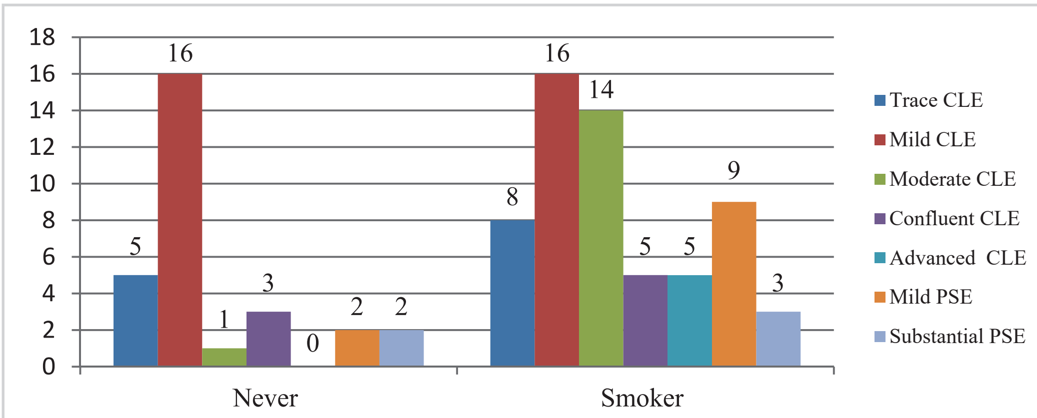

Figure 1. Subtypes of emphysema, smokers

Further, 17.8% of miners had paraseptal emphysema and, moderate centrilobular and severe paraseptal emphysema occurred more often among smokers. Figure 2 and 3 show the realtionships of FVC and FEV as important factors of chronic obstructive pulmonary disease in subtypes of emphysema. Both FVC and FEV1percentage of the surveyed miners was significantly decreased in miners who have advanced destructive centrilobular emphysema ($p < 0.05$).

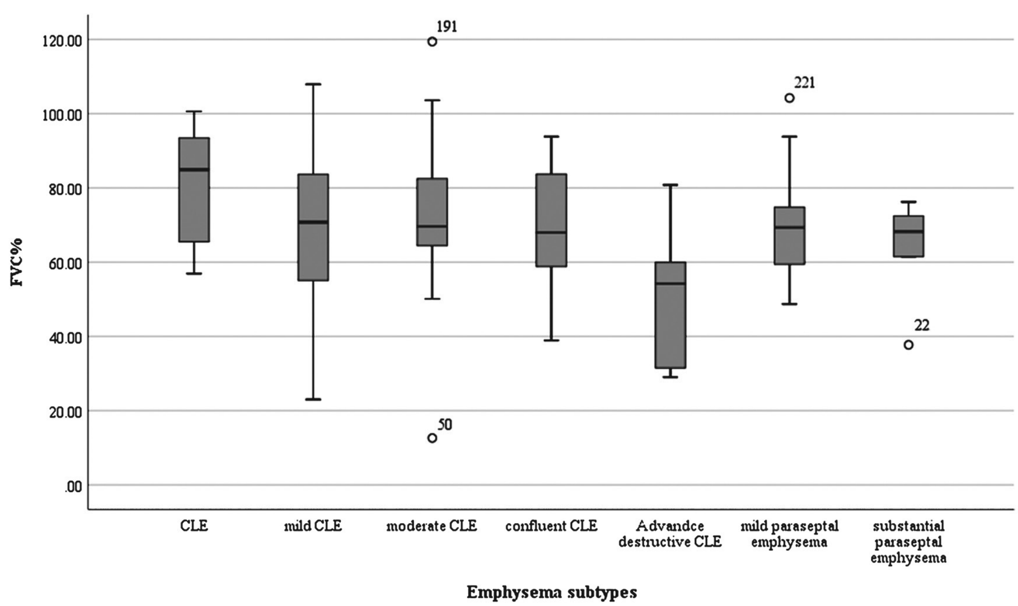

Figure 2. Relationship between subtypes of emphysema and FVC% of miners

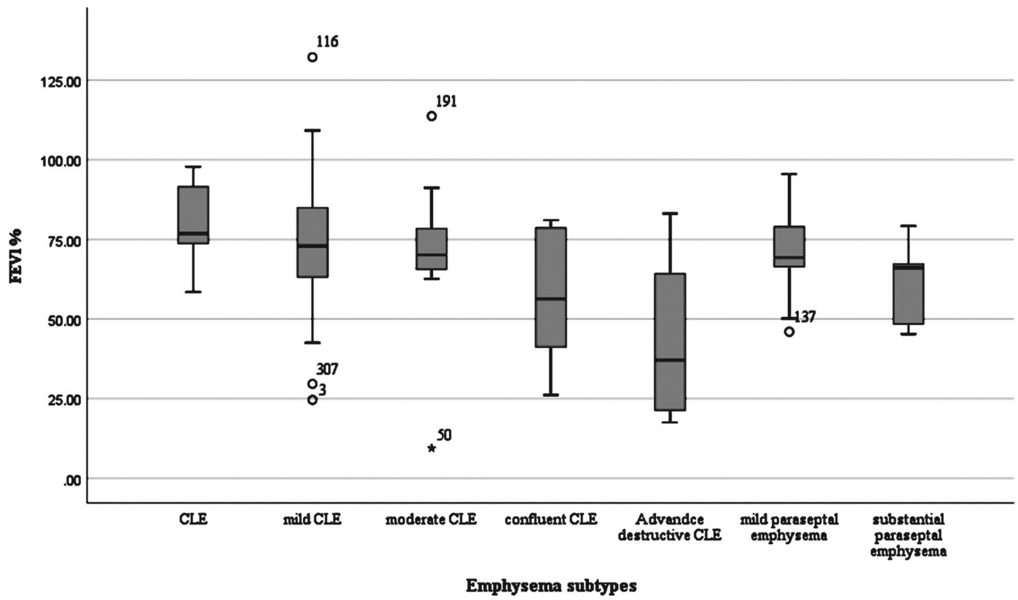

Figure 2. Relationship between subtypes of emphysema and FEV1% of miners

Our study revealed no significant differences in score deviation between LD and standard chest CT (Figure 4 and 5).

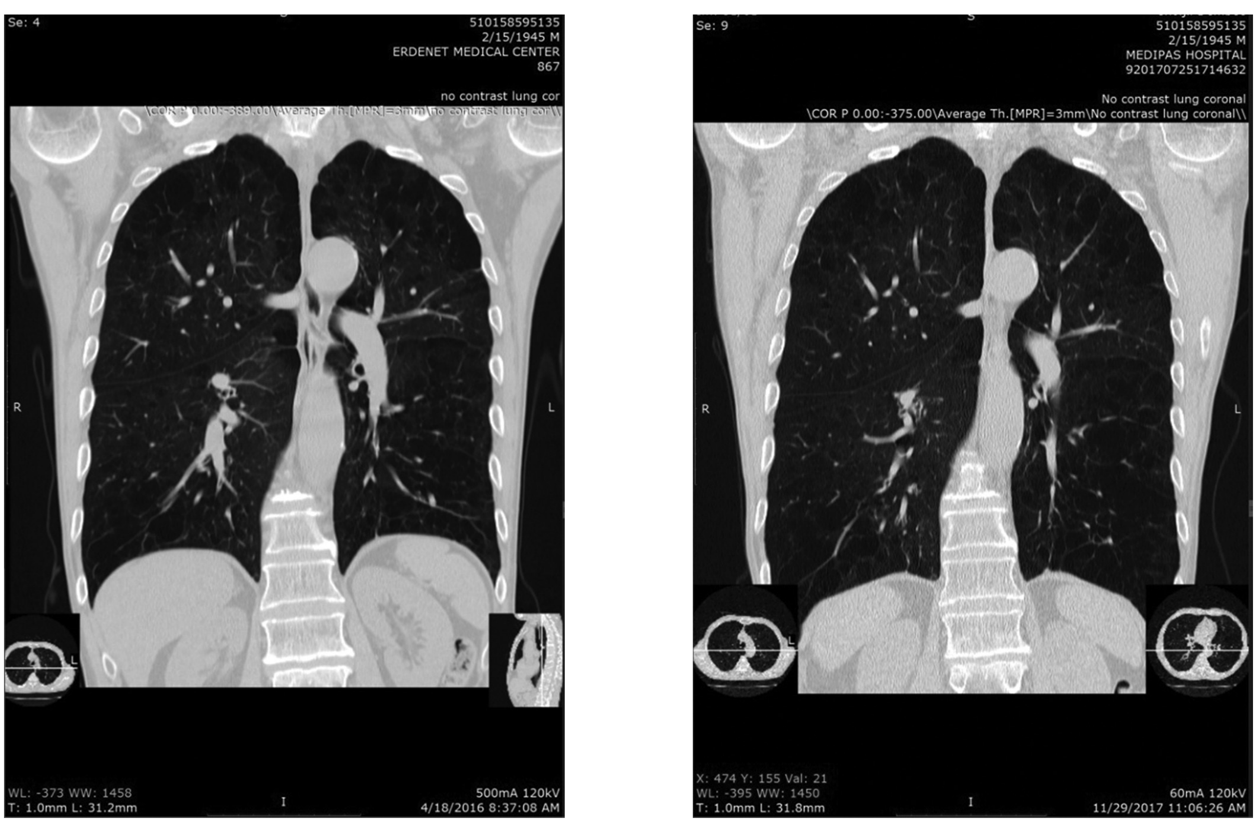

Figure 3. Low-dose and standard chest CT. Moderate centrilobular emphysema

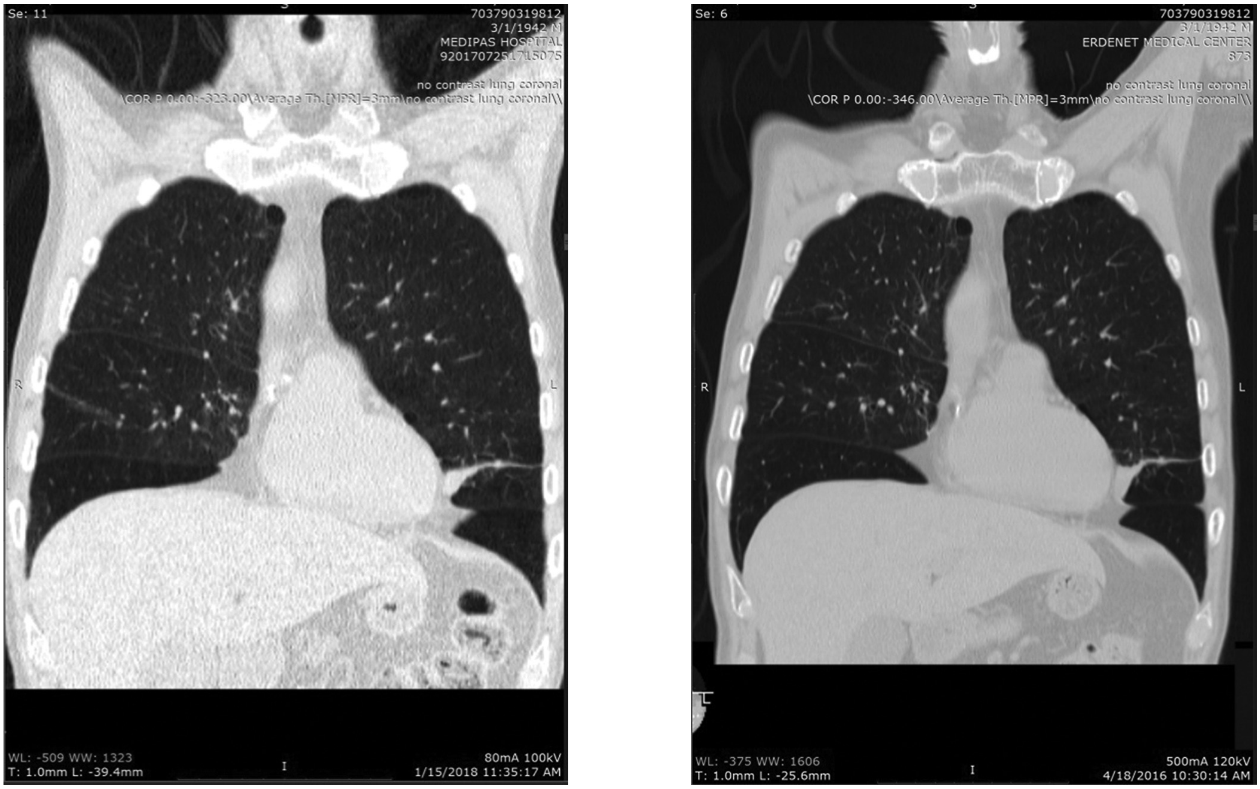

Figure 4. Low-dose and standard chest CT. Mild paraseptal emphysema

In Table 3, the associations of subtypes of emphysema and pulmonary functions are presented. Regarding FEV1 (L) and FVC (L), both non-emphysema and emphysema groups show similar results with the value of 2.0 - 2.7 L. However, the percent predicted by FEV and FVC were significantly different in CLE as well as PSE miners ($p < 0.001$ and $p < 0.002$, respectively), compared to that in non-emphysema miners. In spirometric parameters such as PEFR, VC did not differ significantly between the two groups, while the FEV1/FVC ratio was implicitly decreased in miners those had CLE and PCE. Especially, the FEV1/FVC ratio percentage was below 70% in PCE group miners compared with non-emphysema miners (67.8 vs 81.1 respectively $p < 0.000$).

Table 3. Subtypes of emphysema and pulmonary function

Variables	No emphysema	CLE	PSE	Total	p-value
	N (%)	N (%)	N (%)	N (%)	
FEV1 (L)	2.2 (0.7)	2.1 (0.6)	2.0 (0.6)	6.3 (1.9)	0.576
FEV1% pred	79.4 (21.9)	69.8 (20.9)	67.8 (14.4)	217 (57.2)	0.001
FVC (L)	2.6 (0.8)	2.7 (0.8)	2.6 (0.8)	7.9 (2.4)	0.643
FVC % pred	78.3 (18.1)	70.8 (18.6)	68.4 (15.9)	217(52.6)	0.002
PEFR	4.8 (2.4)	4.3 (2.0)	4.1 (2.4)	13.2 (6.8)	0.209
FEV1/FVC	81.1 (11.4)	73.1 (12.9)	67.8 (10.8)	222 (35.1)	0.000
VC	2.6 (0.8)	2.7 (0.7)	2.6 (0.8)	7.9 (2.3)	0.637

All values shown as mean (standard deviation); FEV1 Forced expiratory volume in the first second; FVC Forced vital capacity; VC Vital capacity; CLE Centrilobular emphysema; PSE paraseptal emphysema

Discussion

Chest radiography does not allow accurate morphologic assessment ofemphysema. The pulmonary emphysema subtypes were assessed by low-dose chest CT scan in miners. In this study, we used visual and quantative character patterns of emphysema in miners (n = 329) using the Fleischner Society classification system.

Visual and quantitative CT evaluation will identify a substantial amount of disease in subjects with mild or absent physiologic evidence of airway obstruction. We showed that the Fleischner classification patterns can be applied to research analysis with good to excellent interobserver agreement.

From studies related to comparing of pulmonary emphysema features of a CT scan with a pathological examination, emphysema was a clinical precursor to serious disorders, such as lung cancer and COPD [24-26]. Therefore, early detection of emphysema in miners working in a dirty environment is important clinically. This study aimed to investigate the relationship between the subtypes of emphysema and smoking and lung functions. In our study, among the 329 miners we found a significant relationship between miners who smoke and lung functions with subtypes of emphysema. It is similar to the survey by Washko GRet al [17]. There were no statistically significant differences in the dusty condition of both emphysema and non-emphysema miners.

Our study revealed 89 (27.1%) emphysema casesamong the surveyed miners. Centrilobular emphysema was found in 73 of the 329 subjects (82.0%) and was either mild or moderate emphysema. This result may be due to the fact that tobacco use is more common among miners.

Wyatt et al[10] first described this pattern, which was subsequently linked to low circulating levels of a1-antitrypsin that are produced by a genetic defect in the a1-antitrypsin gene [11]. In our study, panlobular emphysema was not found. This does not rule outmild panlobular emphysema which may be limited in evaluations by low-dose CT scans. Seventy-five standard chest CT scans were done in this study and did not find a panlobular emphysema case. Also, researchers found that true histologic panlobular emphysema is uncommon in smoking-related emphysema. The Fleischner classification uses the terms "confluent emphysema" and "advanced destructive emphysema" in place of what would previously have been collectively called panlobular emphysema [13].

Advanced destructive subtype emphysema hadsignificant low lung function compared to other types of emphysema. Increasing severity of parenchymal emphysema was associated with progressively increasing airflow obstruction and decreasing oxygen saturation. This result is similar to the David A Lunch et al survey [27] that reported a clear gradient of worsened airflow obstruction and greater respiratory symptoms with increasing emphysema grade, supporting the Fleischner scoring scale as a valid discriminatory tool to assess emphysema severity.

Smokers are 2.6 times more likely to have emphysema than non-smoking miners ($r=2.6$ $p<0.05$). This is similar in comparison to other studies [24,28-30]. In cigarette smokers, mixtures of PLE and CLE can be found within the same lungs. Kim et al have suggested that PLE is less likely to be associated with small airway obstruction than CLE [31]. In our study, PSE and CLE overlap cases were few. Also, Smith et al showed that smokers with predominantly CLE had a higher level of cigarette exposure than those without emphysema [30]. In Mongolia, 27% of the population are active smokers and 42.9% are passive smokers [32].

In addition, morphologic changes of emphysema and airways disease are found in a substantial proportion of subjects who do not meet the spirometric criteria for chronic obstructive pulmonary disease (COPD). This result is the same as the study by Klein JS et al [33].

The CT radiation dose level used for the evaluation of pulmonary emphysema is driven by the balance between radiation dose and image quality. Adequate visual and quantative characterization can be achieved with reduced-dose CT acquisition techniques, as is used for lung cancer screening.

In Mongolia, mining has become the main sector that drives the country's economic growth. The National Statistical Office of Mongolia reported in 2016 that there are 31.000 people engaged actively in the mining indsutry. Despite this high mining population in Mongolia, still there are few studies regarding the health issues encountered by miners. To our knowledge, this is the first study determining the incidence of subtypes of pulmonary emphysemain miners by LDCT. CT may prove to be of great value for evaluating patterns of emphysema by characterization and early discovery of COPD. However, our study is limited by the lack of comparison of the pathology of lung tissues. It is necessary, therefore, to determine in detail the pathological distinctions among miners. Moreover, to increase the power to detect differences with other studies, a bigger sample size would be more efficient. In fact, recent molecular-genetic research studies among miners with COPD have documented an occupational etiology. Thus, in the future, it is essential to also investigate the effects of mining exposure on COPD in Mongolian miners.

Conclusions

We conclude that low dose chest CT can evaluate pulmonary emphysema subtypes by the Fleischner Society classification. Significant association between emphysema and lung function was observed. Dose reduced CT is a useful tool for the assessment of emphysema types..

Conflict of Interest

The authors state no conflict of interest.

Acknowledgments

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