

# Relationships (II) of International Classification of High-resolution Computed Tomography for Occupational and Environmental Respiratory Diseases with ventilatory functions indices for parenchymal abnormalities

Taro TAMURA<sup>1\*</sup>, Narufumi SUGANUMA<sup>2</sup>, Kurt G. HERING<sup>3</sup>, Tapio VEHMAS<sup>4</sup>, Harumi ITOH<sup>5</sup>, Masanori AKIRA<sup>6</sup>, Yoshihiro TAKASHIMA<sup>7</sup>, Harukazu HIRANO<sup>8</sup> and Yukinori KUSAKA<sup>1</sup>

<sup>1</sup>Department of Environmental Health, University of Fukui School of Medicine, Japan

<sup>2</sup>Department of Environmental Medicine, Kochi University School of Medicine, Japan

<sup>3</sup>Department of Diagnostic Radiology, Radiology and Nuclear Medicine, Radiological Clinic, Miners' Hospital, Germany

<sup>4</sup>Department of Radiology, Finnish Institute of Occupational Health, Finland

<sup>5</sup>Department of Radiology, University of Fukui School of Medicine, Japan

<sup>6</sup>Department of Radiology, National Hospital Organization Kinki-Chuo Chest Medical Center, Japan

<sup>7</sup>Department of Surgery, Fukui Saiseikai Hospital, Japan

<sup>8</sup>Koyo Seikyo Hospital, Japan

*Received March 26, 2014 and accepted February 4, 2015*

*Published online in J-STAGE March 26, 2015*

**Abstract:** The International Classification of High-Resolution Computed Tomography (HRCT) for Occupational and Environmental Respiratory Diseases (ICOERD) is used to screen and diagnose respiratory illnesses. Using univariate and multivariate analysis, we investigated the relationship between subject characteristics and parenchymal abnormalities according to ICOERD, and the results of ventilatory function tests (VFT). Thirty-five patients with and 27 controls without mineral dust exposure underwent VFT and HRCT. We recorded all subjects' occupational history for mineral dust exposure and smoking history. Experts independently assessed HRCT using the ICOERD parenchymal abnormalities (Items) grades for well-defined rounded opacities (RO), linear and/or irregular opacities (IR), and emphysema (EM). High-resolution computed tomography showed that 11 patients had RO; 15 patients, IR; and 19 patients, EM. According to the multiple regression model, age and height had significant associations with many indices ventilatory functions such as vital capacity, forced vital capacity, and forced expiratory volume in 1 s (FEV<sub>1</sub>). The EM summed grades on the upper, middle, and lower zones of the right and left lungs also had significant associations with FEV<sub>1</sub> and the maximum mid-expiratory flow rate. The results suggest the ICOERD notation is adequate based on the good and significant multiple regression modeling of ventilatory function with the EM summed grades.

**Key words:** Environmental lung disease, High-resolution computed tomography, Emphysema, Occupational lung disease, Ventilatory function, Silicosis, Asbestosis, FEV<sub>1</sub>

\*To whom correspondence should be addressed.

E-mail: tarou@u-fukui.ac.jp

©2015 National Institute of Occupational Safety and Health

## Introduction

We recently established a correlation between the International Classification of High-Resolution Computed Tomography for Occupational and Environmental Diseases (ICOERD)<sup>1)</sup> and readings of chest X-rays according to the International Labor Organization Classification/International Classification of Radiographs of Pneumoconioses (ILO/ICRP) in patients with pneumoconiosis<sup>2)</sup>. We have already reported the reliability of the selection of reference films for ICOERD and of multiple readers' records using the ICOERD<sup>3, 4)</sup>. Since the publication of those papers, the ICOERD has been used for many purposes, including diagnosis, epidemiological reporting, and screening of respiratory diseases<sup>5-9)</sup>.

Emphysema in association with pneumoconiosis (e.g., silicosis and asbestosis) can be detected by high-resolution computed tomography (HRCT)<sup>10, 11)</sup>. Previous studies have investigated the relationship between the findings of HRCT and ventilatory function<sup>7, 11-14)</sup>. The authors of those studies used different classifications from the current ICOERD, or used Finnish original classifications, which were previously harmonized into the ICOERD<sup>11-14)</sup>. Vierikko *et al.*<sup>7)</sup> reported that ventilatory function is associated with the presence or absence of interstitial lung fibrosis on HRCT, based on a similar classification. On the other hand, we used the summed grades as an ordinal scale, based on the ICOERD. We described the details of the procedure to calculate the summed grades according to the ICOERD. We studied the effects of parenchymal lesions on ventilatory function in terms of the summed grades of the readings of HRCT.

Ventilatory function tests are used to assess the physiological severity of many respiratory diseases. For instance, respiratory failure is a complication of severe pneumoconiosis<sup>15)</sup>. Gaik and Ooi reported that impaired lung function is caused by progressive massive fibrosis (PMF), mixed-dust fibrosis (MDF), and emphysema<sup>16)</sup>. Piirilä *et al.* also reported that the most important factor determining the degree of functional impairment in smoking, asbestos-exposed workers was the presence of pulmonary emphysema<sup>13)</sup>. Patients with low grade or early stage asbestosis did not suffer from ventilatory failure but presented mild symptoms and impairment of ventilatory function. Ventilatory function tests are compulsorily in the assessment of the severity of pneumoconiosis, according to the Japan Pneumoconiosis Law<sup>17)</sup>, and internationally, they are used for evaluating air flow limitations in chronic obstructive pulmonary disease (COPD), according to the global initiative for chronic ob-

structive lung disease (GOLD)<sup>18)</sup>.

As stated above, pneumoconiosis is associated with the impairment of ventilatory function. In patients with large opacities, emphysema, and bronchiectasis, the ventilatory function is further impaired. These parenchymal findings are included in the ICOERD criteria and system. In the present study, we evaluated the adequacy of the ICOERD notation, based on the association between reading results based on the ICOERD and ventilatory function.

## Subjects and Methods

### Subjects

The subjects included in this study were the same as in our previous paper<sup>2)</sup>. However, not all subjects underwent a ventilatory function test. As a result, this study's subjects were 35 patients with and 27 control participants without occupational exposure to mineral dust. For all individuals, experts recorded the individuals' occupational exposure history and smoking history, which included smoking status (e.g. current smoker, ex-smoker, non-smoker; average number of cigarettes smoked per day, and the number of years of consumption). Patients were selected from among patients developing pneumoconiosis due to substantial mineral dust exposure who were attending a hospital in Fukui Prefecture, Japan. There were 34 current smokers, 25 ex-smokers, and 3 non-smokers. The median total years of mineral dust exposure history among the patients was 31 yr (range, 5–52 yr).

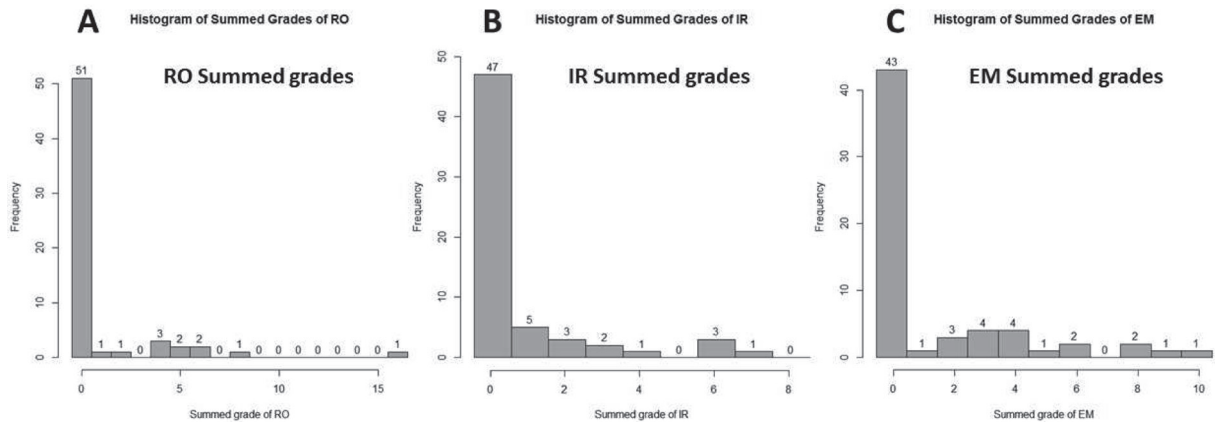
All the study participants provided their written, informed consent after the risks and benefits of HRCT explained to them. Each participant underwent HRCT and VFT on the same day. The study protocol was approved by the ethics review board of the University of Fukui School of Medicine (Fukui, Japan).

### Radiological examinations

The subjects underwent HRCT examinations, as described in our previous paper<sup>2)</sup>.

### Ventilatory function

Ventilatory function was assessed by using a hot-wire anemometer-type spirometer (Riko AS500, Japan) in accordance with the international standards of the American Thoracic Society/European Respiratory Society (ATS/ERS)<sup>19)</sup>. The following items were measured for all subjects: vital capacity (VC) (l); VC as percent of predicted VC, according to Baldwin [%VC (B)]<sup>20)</sup>; VC as percent of predicted VC, according to the Japan Respiratory Society (JRS)<sup>21)</sup> [%VC



**Fig. 1.** Distribution of the median summed grades among the 3 readers of the Items according to the International Classification of High-Resolution Computed Tomography for Occupational and Environmental Respiratory Diseases, for (A) well-defined rounded opacities (RO), (B) irregular and/or linear opacities (IR), and (C) emphysema (EM).

(J)<sup>21</sup>]; forced vital capacity (FVC) (I); FVC as percent of predicted VC, according to Baldwin [%FVC (B)]; FVC as percent of predicted FVC, according to JRS [%FVC (J)]; forced expiratory volume in 1 s (FEV<sub>1</sub>) (I); FEV<sub>1</sub> as percent of FVC [FEV<sub>1</sub>%]; FEV<sub>1</sub> as percent of predicted FEV<sub>1</sub>, according to JRS [%FEV<sub>1</sub>]; maximum mid-expiratory flow rate (MMF) (l/min); and peak expiratory flow (PEF) (l/min).

#### Trial reading

Three experts who had been engaged in the development of the ICOERD independently assessed the HRCT findings in accordance with the ICOERD. The ICOERD uses 4-point categories to quantify the grades of parenchymal lesions (Items) such as well-defined rounded opacities (RO), irregular and/or linear opacities (IR), emphysema (EM), ground glass opacities (GGO), and honeycombing (HC) in the upper, middle, and lower zones of the right and left lungs. The summed grades are calculated for each of the Items of the parenchymal abnormalities (i.e., RO, IR, EM, GGO, and HC) by adding the scores of each of the 6 zones. In our previous study, we described in detail the procedure for calculating the summed grades of the Items according to the ICOERD<sup>2</sup>.

For the present analysis, we used the median reading of the summed grades of the ICOERD Items, as described in our previous study<sup>2</sup>. We considered the median of the summed grades of 1 or more as indicative of the presence of Items.

We classified the patients into groups, based on each of the summed grades on a 19-point scale. We named the groups as the “summed grade” groups. We re-classified the summed grade groups into “Score groups” because the

number of patients (based on the summed grades of RO, IR or EM) was low for some “summed grade” groups. The score included a particular range of summed grades for each. The patients in the summed grade 0 group were classified as an independent group in the “Score 0 group” because the patients did not have any abnormal Items. Because patients in the RO summed grade groups of 1 or greater had a very wide distribution (Fig. 1), we classified the patients in RO summed grade groups 1–4 as “RO Score 1 group” and patients in RO summed grade groups 5 or greater as “RO Score 2 group”. We classified patients in IR summed grade groups 1–2 as “IR Score 1 group”; IR summed grade groups 3–4 as “IR Score 2 group”; and IR summed grade groups 5 or greater as “IR Score 3 group.” We classified patients in EM summed grade groups 1–2 as “EM Score 1 group”; EM summed grade groups 3–4 as “EM Score 2 group”; EM summed grade groups 5–6 as “EM Score 3 group”; and EM summed grades group 7 or greater as “EM Score 4 group.”

#### Statistical analysis

One-way analysis of variance (ANOVA) was used to evaluate the differences in the results of ventilatory functions as objective variables using the ICOERD Items Score groups for each as explanatory variables. In the analysis, we used age, height, mineral dust exposure, and pack-year as the dependent variables because we presumed these variables would affect ventilatory functions in the multiple regression model described later. A *post hoc* comparison of the means was performed using the Tukey-Kramer test for multiple comparisons. Multiple regression analysis of ventilatory functions as dependent variables was performed with relevant factors as independent variables. A value of

$p < 0.05$  was considered significant for the ANOVA, *post hoc* multiple comparison, and multiple regression analysis. For all analyses, we used the software package R (version 2.11.1) by the R Foundation for Statistical Computing (Vienna, Austria) (<http://www.r-project.org/foundation/>).

## Results

### Ventilatory function

The mean and standard deviation of VC, %VC (B), %VC (J), FVC, %FVC (B), %FVC (J), FEV<sub>1</sub>, FEV<sub>1</sub>%, %FEV<sub>1</sub>, MMF, and PEF were  $3.35 \pm 0.97$  l,  $96.97 \pm 22.89\%$ ,  $88.49 \pm 19.24\%$ ,  $3.31 \pm 0.96$  l,  $95.89 \pm 22.51\%$ ,  $87.51 \pm 18.99\%$ ,  $2.48 \pm 0.84$  l,  $73.72 \pm 12.4\%$ ,  $80.62 \pm 21\%$ ,  $2.07 \pm 1.09$  l/min, and  $6.48 \pm 2.73$  l/min, respectively (Table 1).

### Reading results of the 3 readers, based on the ICOERD

Based on the median values of the summed grades for each Items with a cut-off of 1 or more, there were 11 patients with RO, 15 patients with IR, 19 patients with EM, 0 patients with GGO, and 1 patient with HC. The distributions of the median summed grades of RO, IR, and EM are shown in Fig. 1. The median summed grades of HC and GGO were removed from the subsequent analysis because the number of patients with HC or GGO was very small.

### The results of ANOVA

We analyzed the results of the VFT of the Score groups of the ICOERD Items by ANOVA. Tables 2–4 show the results. There were statistically significant differences in the RO score groups means of age, mineral dust exposure, FVC, and FEV<sub>1</sub>, as determined by one-way ANOVA (Table 2). Based on multiple comparisons, the mineral dust exposure had a significantly lower mean in RO Score 0 group than in RO Score 1 group and RO Score 2 group. However, the means of age, FVC, and FEV<sub>1</sub> of the RO score groups were not significantly different, according to the multiple comparison. There was a statistically significant difference among the IR score groups' means of mineral dust exposure, as determined by one-way ANOVA (Table 3). According to the multiple comparison, mineral dust exposure had a significantly lower mean in IR Score 0 group than in IR Score 3 group. There were statistically significant differences among the EM score groups' means of age, pack-year, FEV<sub>1</sub>, FEV<sub>1</sub>%, %FEV<sub>1</sub>, MMF and PEF, as determined by one-way ANOVA (Table 4). The mean age did not significant differences among the EM score groups, according to the multiple comparison, but the pack-year had a significantly higher mean in EM Score 2 group than for the

**Table 1. Results of the ventilatory function tests**

	Mean $\pm$ SD	(Range)
VC (l)	$3.35 \pm 0.97$	(1.58–6.36)
%VC (B) (%)	$96.97 \pm 22.89$	(52.10–153.77)
%VC (J) (%)	$88.49 \pm 19.24$	(48.53–128.12)
FVC (l)	$3.31 \pm 0.96$	(1.13–6.07)
%FVC (B) (%)	$95.89 \pm 22.51$	(37.26–146.76)
%FVC (J) (%)	$87.51 \pm 18.99$	(36.92–122.28)
FEV <sub>1</sub> (l)	$2.48 \pm 0.84$	(0.27–4.88)
FEV <sub>1</sub> % (%)	$73.72 \pm 12.40$	(11.84–100.00)
%FEV <sub>1</sub> (%)	$80.62 \pm 21.00$	(8.23–117.60)
MMF (l/min)	$2.07 \pm 1.09$	(0.09–4.69)
PEF (l/min)	$6.48 \pm 2.73$	(0.96–12.46)

ANOVA: analysis of variance; EM: emphysema; Exposure: total years of mineral-dust exposure; FEV<sub>1</sub>: forced expiratory volume in 1 s; %FEV<sub>1</sub>: FEV<sub>1</sub> as percent of predicted FEV<sub>1</sub> according to Japan Respiratory Society (JRS) method; FEV<sub>1</sub>%: FEV<sub>1</sub> as percent of forced vital capacity; FVC: forced vital capacity; %FVC (B): FVC as percent of predicted vital capacity according to Baldwin method; %FVC (J): FVC as percent of predicted FVC according to the JRS method; Grade: summed grades according to the ICOERD; ICOERD: International Classification of High-Resolution Computed Tomography for Environmental and Occupational Respiratory Diseases; IR: irregular and/or linear opacities; MMF: maximum mid-expiratory flow rate; Pack-year: (the number of cigarettes smoked per day  $\times$  number of years smoked)/20; PEF: peak expiratory flow; RO: well-defined rounded opacities; Score group: re-classified group from the summed grades; VC: vital capacity; %VC (B): VC as percent of predicted VC according to the Baldwin method; %VC (J): VC as percent of predicted VC according to the JRS method.

EM Score 0 group. Figures 2 and 3 show the results of the multiple comparison of the ventilatory functions of FEV<sub>1</sub> and FEV<sub>1</sub>%, respectively. The %FEV<sub>1</sub>, MMF, and PEF as well as FEV<sub>1</sub> had significantly lower means in EM Score 4 group than in EM Score 0 group.

### Results of multiple regression analysis

The results of ANOVA suggested a relationship between total years of occupational mineral dust exposure and the score of RO or IR. In addition, RO or IR on HRCT were considered to be caused by the mineral dust exposures of the patients. We therefore excluded mineral dust exposure from the dependent variables. Age, height, and smoking history are well-known factors affecting ventilatory function. Therefore, we made the following model on the basis of the collective inclusion of the following variables and analyzed the effects of the ICOERD Items on ventilatory functions.

Each ventilatory function =  $a_1 \times \text{Age} + a_2 \times \text{Height} + a_3 \times \text{Pack-year} + a_4 \times \text{Score of RO} + a_5 \times \text{Score of IR} + a_6 \times \text{Score of EM}$ .

Tables 5 and 6 show the results of the multiple regres-

**Table 2. Association of the patients' characteristics and ventilatory functions with the RO score groups**

	RO score group			p-value
	0 (Grade 0)	1 (Grades 1–4)	2 (Grades 5 or greater)	
n	51	5	6	
Age	60.4 ± 8.5	68.2 ± 6.9	67.0 ± 5.1	0.037*
Height	165.8 ± 7.2	160.7 ± 4.9	161.4 ± 4.1	0.123
Pack-year	33.0 ± 21.5	35.8 ± 35.2	38.8 ± 34.3	0.842
Exposure	13.3 ± 16.2 <sup>#</sup>	34.5 ± 7.9 <sup>#</sup>	36.8 ± 4.4 <sup>#</sup>	<0.001*
VC	3.49 ± 0.99	2.79 ± 0.75	2.67 ± 0.44	0.059
%VC (B)	99.7 ± 23.3	86.7 ± 22.1	82.1 ± 11.2	0.116
%VC (J)	90.5 ± 19.6	81.7 ± 20.5	75.8 ± 9.0	0.183
FVC	3.45 ± 0.96	2.86 ± 0.78	2.52 ± 0.55	0.039*
%FVC (B)	98.8 ± 22.3	88.7 ± 22.3	77.2 ± 14.5	0.061
%FVC (J)	89.7 ± 18.9	83.5 ± 21.3	72.3 ± 11.7	0.091
FEV <sub>1</sub>	2.60 ± 0.82	1.89 ± 0.90	1.90 ± 0.51	0.038*
FEV <sub>1</sub> %	74.6 ± 11.3	62.8 ± 16.0	75.7 ± 15.9	0.116
%FEV <sub>1</sub>	83.2 ± 20.0	69.3 ± 31.3	68.4 ± 15.1	0.120
MMF	2.16 ± 1.05	1.32 ± 1.24	1.97 ± 1.22	0.257
PEF	6.80 ± 2.74	4.32 ± 1.43	5.49 ± 2.73	0.098

See Table 1 for abbreviations. The p-values were calculated using one-way analysis of variance. \*p<0.05. <sup>#</sup>According to the Tukey-Kramer multiple comparison, exposure had a significantly lower mean in the RO Score 0 group than in the RO Score 1 and 2 groups.

**Table 3. Association of patients' characteristics and ventilatory functions with the IR score groups**

	IR score group				p-value
	0 (Grade 0)	1 (Grades 1–2)	2 (Grades 3–4)	3 (Grade 5 or greater)	
n	47	8	3	4	
Age	60.2 ± 8.7	64.6 ± 6.5	67.0 ± 5.3	69.3 ± 3.9	0.076
Height	166.0 ± 7.2	162.6 ± 4.8	164.8 ± 8.5	157.8 ± 2.2	0.102
Pack-year	30.4 ± 9.8	38.5 ± 32.8	55.0 ± 32.8	48.2 ± 38.9	0.161
Exposure	14.9 ± 16.8 <sup>#</sup>	15.4 ± 17.1	34.0 ± 7.9	37.4 ± 6.2 <sup>#</sup>	0.021*
VC	3.49 ± 1.01	3.12 ± 0.78	2.75 ± 0.87	2.61 ± 0.36	0.176
%VC (B)	99.7 ± 23.5	93.8 ± 22.2	81.9 ± 20.9	83.2 ± 8.7	0.317
%VC (J)	90.3 ± 19.9	86.8 ± 19.6	75.0 ± 16.3	80.0 ± 7.5	0.441
FVC	3.45 ± 0.99	3.14 ± 0.69	2.67 ± 0.87	2.50 ± 0.44	0.131
%FVC (B)	98.6 ± 23.1	94.6 ± 19.5	79.5 ± 21.6	79.3 ± 12.0	0.219
%FVC (J)	89.4 ± 19.6	87.7 ± 17.2	72.8 ± 17.3	76.5 ± 10.8	0.315
FEV <sub>1</sub>	2.59 ± 0.86	2.37 ± 0.49	1.81 ± 1.02	1.82 ± 0.61	0.145
FEV <sub>1</sub> %	74.6 ± 12.6	76.0 ± 5.8	63.3 ± 21.3	66.1 ± 10.3	0.249
%FEV <sub>1</sub>	82.3 ± 20.8	82.8 ± 16.2	60.9 ± 30.1	70.8 ± 23.1	0.272
MMF	2.23 ± 1.13	1.98 ± 0.79	1.34 ± 0.91	1.02 ± 0.40	0.103
PEF	6.74 ± 2.77	6.12 ± 2.48	5.53 ± 3.31	4.85 ± 2.55	0.516

See Table 1 for abbreviations. IR: irregular and/or linear opacities. <sup>#</sup>According to Tukey-Kramer multiple comparison, exposure had a significantly lower mean in the IR Score 0 group than in the IR Score 3 group.

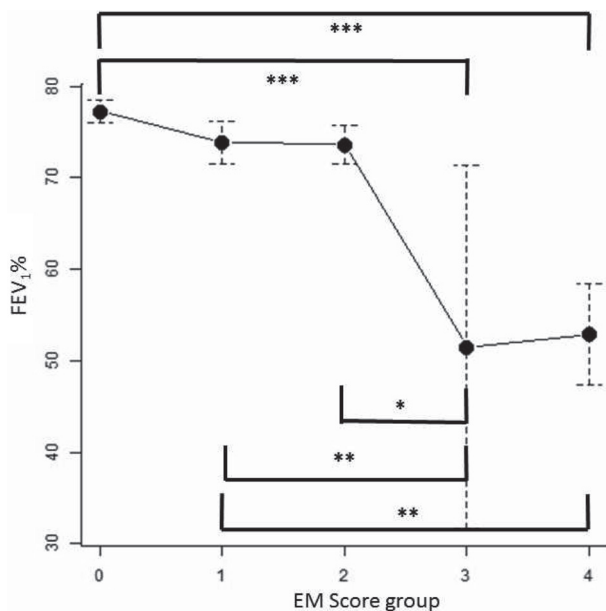
sion analysis. The residual error had normal distribution. Table 5 shows the relationships between the independent factors and the restrictive respiratory disorders of each

factor (e.g. VC and FVC). Table 6 shows the relationships between the independent factors and obstructive respiratory disorders of each factor (e.g. FEV<sub>1</sub> and PEF). Age

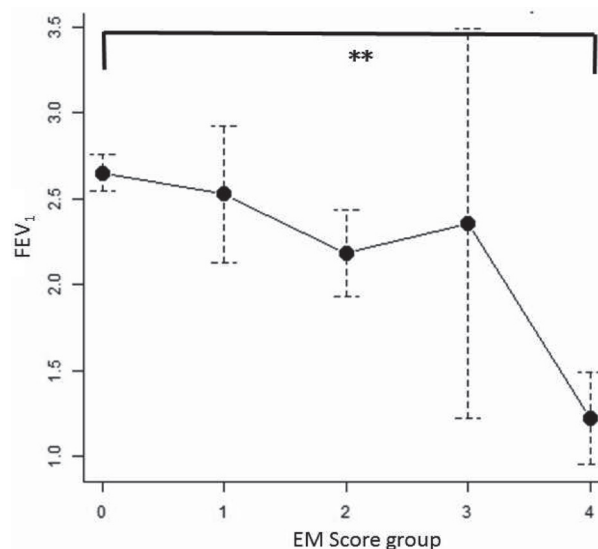
**Table 4.** Association of patients' characteristics and ventilatory function with the EM score groups

	EM Score group					<i>p</i> -value
	0 (Grade 0)	1 (Grade 1–2)	2 (Grade 3–4)	3 (Grade 5–6)	4 (Grade 7 or greater)	
n	43	4	8	3	4	
Age	60.1 ± 8.2	61.8 ± 11.1	67.9 ± 5.1	57.7 ± 10.1	69.3 ± 5.1	0.041*
Height	164.5 ± 6.9	166.6 ± 7.1	164.6 ± 6.6	175.0 ± 2.6	161.5 ± 7.04	0.102
Pack-year	26.9 ± 17.3 <sup>#</sup>	36.4 ± 15.1	62.0 ± 34.2 <sup>#</sup>	35.0 ± 13.2	47.6 ± 32.9	0.001*
Exposure	16.4 ± 17.3	16.4 ± 19.0	18.3 ± 18.4	7.2 ± 12.5	33.7 ± 7.1	0.307
VC	3.44 ± 0.91	3.37 ± 1.19	3.17 ± 0.96	3.84 ± 1.78	2.36 ± 0.47	0.238
%VC (B)	99.1 ± 20.6	96.5 ± 29.3	95.5 ± 26.6	102.2 ± 42.4	73.6 ± 13.0	0.317
%VC (J)	90.7 ± 17.3	86.8 ± 24.1	87.2 ± 22.0	88.3 ± 36.5	69.2 ± 12.4	0.329
FVC	3.42 ± 0.86	3.43 ± 1.03	3.01 ± 1.07	3.89 ± 1.64	2.23 ± 0.55	0.099
%FVC (B)	98.6 ± 19.3	98.4 ± 24.0	90.3 ± 30.0	103.7 ± 38.1	69.3 ± 16.1	0.127
%FVC (J)	90.3 ± 16.3	88.5 ± 18.3	82.3 ± 25.4	89.5 ± 32.6	65.4 ± 15.5	0.134
FEV <sub>1</sub>	2.65 ± 0.69 <sup>##</sup>	2.53 ± 0.79	2.18 ± 0.71	2.36 ± 1.96	1.22 ± 0.54 <sup>##</sup>	0.013*
FEV <sub>1</sub> %	77.2 ± 7.9 <sup>##</sup>	73.8 ± 4.6	73.6 ± 6.0	51.5 ± 34.4	52.9 ± 11.0 <sup>##</sup>	<0.001*
%FEV <sub>1</sub>	86.0 ± 15.0 <sup>##</sup>	80.6 ± 15.5	75.5 ± 21.3	64.7 ± 51.0	45.3 ± 19.6 <sup>##</sup>	0.001*
MMF	2.38 ± 1.05 <sup>##</sup>	1.79 ± 0.76	1.42 ± 0.83	1.63 ± 1.36	0.69 ± 0.34 <sup>##</sup>	0.006*
PEF	7.01 ± 2.21 <sup>##</sup>	5.59 ± 3.89	5.56 ± 2.67	7.10 ± 5.79	2.99 ± 2.18 <sup>##</sup>	0.041

See Table 1 for abbreviations. <sup>#</sup> According to the multiple comparison, pack-year had a significantly higher mean in the EM Score 2 group than in the EM Score 0 group. <sup>##</sup> According to the multiple comparison, FEV<sub>1</sub>, %FEV<sub>1</sub>, MMF and PEF of the EM Score 4 group had significantly lower means than those of the EM Score 0 group. See Figs. 2 and 3.

**Fig. 2.** The mean FEV<sub>1</sub>% for each score of EM.

EM: emphysema; FEV<sub>1</sub>%, percent of forced vital capacity; Score group: re-classified group from the summed grades according to the ICOERD. The error bars represent the standard error of the mean (SEM) for each bar. The statistical significance was calculated using one-way analysis of variance (ANOVA), followed by the Tukey–Kramer multiple comparison test. \**p*<0.05, \*\**p*<0.01, and \*\*\**p*<0.001.

**Fig. 3.** The mean FEV<sub>1</sub> for each EM Score group.

EM: emphysema; FEV<sub>1</sub>: forced expiratory volume in 1 second; Score group: re-classified group from the summed grades according to the ICOERD. The error bars represent the standard error of the mean (SEM) for each bar. Statistical significance was calculated using one-way analysis of variance (ANOVA), followed by the Tukey–Kramer multiple comparison test. \**p*<0.05, \*\**p*<0.01, and \*\*\**p*<0.001.

**Table 5. Multiple regression analysis of the relationships of restrictive ventilatory function collectively with the patients' characteristics and scores of ICOERD Items**

	$\beta$ -Values of ventilatory functions					
	VC	%VC (B)	%VC (J)	FVC	%FVC (B)	%FVC (J)
Intercepts	-3.47 <sup>ns</sup> (2.58)	-39.16 <sup>ns</sup> (74.8)	44.4 <sup>ns</sup> (68.7)	-3.62 <sup>ns</sup> (2.47)	-45.0 <sup>ns</sup> (71.9)	38.4 <sup>ns</sup> (66.2)
Age	-0.053 <sup>***</sup> (0.011)	-0.912 <sup>**</sup> (0.33)	-0.76 <sup>*</sup> (-0.3)	-0.05 <sup>***</sup> (0.01)	-0.831 <sup>*</sup> (0.932)	-0.687 <sup>*</sup> (0.294)
Height	0.062 <sup>***</sup> (0.014)	1.2 <sup>**</sup> (0.39)	0.58 <sup>ns</sup> (0.36)	0.062 <sup>***</sup> (0.013)	1.21 <sup>**</sup> (0.38)	0.595 <sup>ns</sup> (0.349)
Pack-year	-0.0037 <sup>ns</sup> (0.0038)	-0.127 <sup>ns</sup> (0.11)	-0.12 <sup>ns</sup> (0.1)	-0.0043 <sup>ns</sup> (0.003)	-0.144 <sup>ns</sup> (0.107)	-0.140 <sup>ns</sup> (0.098)
RO Score group	-0.099 <sup>ns</sup> (0.15)	-3.12 <sup>ns</sup> (4.31)	-3.02 <sup>ns</sup> (3.97)	-0.138 <sup>ns</sup> (0.14)	-4.42 <sup>ns</sup> (4.15)	-4.25 <sup>ns</sup> (3.82)
IR Score group	0.086 <sup>ns</sup> (0.12)	2.38 <sup>ns</sup> (3.43)	2.22 <sup>ns</sup> (3.15)	0.09 <sup>ns</sup> (0.11)	2.51 <sup>ns</sup> (3.3)	2.41 <sup>ns</sup> (3.03)
EM Score group	-0.055 <sup>ns</sup> (0.078)	-1.78 <sup>ns</sup> (2.27)	-1.69 <sup>ns</sup> (2.08)	-0.079 <sup>ns</sup> (0.075)	-2.58 <sup>ns</sup> (2.18)	-2.42 <sup>ns</sup> (2.01)
Statistic	$R^2=0.61$	$R^2=0.40$	$R^2=0.29$	$R^2=0.62$	$R^2=0.42$	$R^2=0.32$
Summary	F=14.07 <sup>***</sup>	F=6.099 <sup>***</sup>	F=3.66 <sup>**</sup>	F=15.26 <sup>***</sup>	F=6.86 <sup>***</sup>	F=4.288 <sup>**</sup>

See Table 1 for abbreviations. ns: not significant. \* $p<0.05$ , \*\* $p<0.01$ , and \*\*\* $p<0.001$ .

and height were significant independent factors of both respiratory functions, according to the multiple regression analysis. The emphysema score was a significant independent factor of obstructive respiratory disorders. However, none of the other ICOERD Items were significant independent factors of restrictive respiratory disorders.

## Discussion

The subjects of this study had parenchymal findings on HRCT at low Item grades and the normal range of VFT, probably because we enrolled workers with slight to mild mineral dust exposure. It was considered reasonable by us that the target population had early stage pneumoconiosis because HRCT is useful for detecting early stage pneumoconiosis<sup>22</sup>. If we had recruited more patients with slight to severe pneumoconiosis, we would have established a definite association between HRCT findings (Items) and ventilatory function test results.

Age and height are well-known predictors of pulmonary restrictive disorders (e.g. VC and FVC) and pulmonary obstructive disorders (e.g. FEV<sub>1</sub> and %FEV<sub>1</sub>). These indices were also adopted as significant predictors in the present study, and the prediction equations with these indices were analogous to the prediction equations of the JRS.

Piirilä *et al.* reported that in asbestos-exposed smoking workers, FEV<sub>1</sub>% negatively correlated with emphysema

type of CT<sup>12</sup>), and that emphysema was the most important factor determining the degree of ventilatory functional impairment<sup>13</sup>. In the present study, the score of EM summed grades was adopted as a significant predictor of pulmonary obstructive disorders (e.g. FEV<sub>1</sub> and %FEV<sub>1</sub>), based on multiple regression analysis.

Meijer *et al.*<sup>5</sup>) reported the association between the reading results of HRCT, according to the ICOERD and ventilatory function; the presence of IR, but not RO, was significantly associated with ventilatory function (i.e. FVC and FEV<sub>1</sub>). On the other hand, in the present study, the scores of neither RO nor IR had a significant relationship with ventilatory functions according to multiple regression analysis. Because there were statistically significant differences between the RO score groups means of FVC and FEV<sub>1</sub>, as determined by ANOVA, the score of RO rather than the score of IR may have a relationship with ventilatory function impairment in the slight to severe stages of pneumoconiosis. The results of the present study suggest that RO was the cause of the deterioration of the ventilatory function of the mineral dust-exposed workers, which is different from the study of Meijer *et al.*, which suggested IR was the cause of its deterioration among construction workers.

We offer some reasons for the difference. First, there were differences in the actual procedures of grading Items. Second, there were differences in subjects, especially in the severity of pneumoconiosis. Third, there were dif-

**Table 6. Multiple regression analysis of the relationships of obstructive ventilatory functions collectively with patients' characteristics and scores of the ICOERD Items**

	$\beta$ -Values of ventilatory functions				
	FEV <sub>1</sub>	FEV <sub>1</sub> %	%FEV <sub>1</sub>	MMF	PEF
Intercepts	-0.653 <sup>ns</sup> (2.13)	152 <sup>***</sup> (41.1)	81.3 <sup>ns</sup> (69.1)	5.66 <sup>ns</sup> (3.15)	-2.74 <sup>ns</sup> (9)
Age	-0.05 <sup>***</sup> (0.0095)	-0.39 <sup>*</sup> (0.18)	-0.75 <sup>*</sup> (0.31)	-0.073 <sup>***</sup> (0.014)	-0.125 <sup>**</sup> (0.04)
Height	0.039 <sup>**</sup> (0.011)	-0.31 <sup>ns</sup> (0.22)	0.32 <sup>ns</sup> (0.36)	0.0073 <sup>ns</sup> (0.017)	0.106 <sup>*</sup> (0.047)
Pack-year	-0.0025 <sup>ns</sup> (0.0032)	0.023 <sup>ns</sup> (0.061)	-0.11 <sup>ns</sup> (0.1)	-0.0032 <sup>ns</sup> (0.0047)	-0.0083 <sup>ns</sup> (0.013)
RO Score group	-0.097 <sup>ns</sup> (0.12)	1.63 <sup>ns</sup> (2.37)	-4.14 <sup>ns</sup> (3.99)	0.248 <sup>ns</sup> (0.182)	-0.199 <sup>ns</sup> (0.52)
IR Score group	0.12 <sup>ns</sup> (0.098)	-0.077 <sup>ns</sup> (1.89)	3.83 <sup>ns</sup> (3.17)	-0.0813 <sup>ns</sup> (0.145)	0.425 <sup>ns</sup> (0.413)
EM Score group	-0.19 <sup>**</sup> (0.064)	-4.92 <sup>***</sup> (1.24)	-6.77 <sup>**</sup> (2.1)	-0.238 <sup>*</sup> (0.096)	-0.542 <sup>ns</sup> (0.273)
Statistic Summary	R <sup>2</sup> =0.636 F=15.99 <sup>***</sup>	R <sup>2</sup> =0.384 F=5.725 <sup>***</sup>	R <sup>2</sup> =0.392 F=5.913 <sup>***</sup>	R <sup>2</sup> =0.531 F=10.39 <sup>***</sup>	R <sup>2</sup> =0.389 F=5.843 <sup>***</sup>

See Table 1 for abbreviations. ns: not significant. \* $p < 0.05$ , \*\* $p < 0.01$ , and \*\*\* $p < 0.001$ .

ferences in mineral dust exposures, because we focused on mild pneumoconiosis cases in the current study. Also, the sampled number may not have been sufficiently high enough to study the relationships between RO or IR and ventilatory function, and we should have tried to recruit more patients of each grade.

We used the ICOERD to differentiate each Item. The EM score was adopted as a significant predictor of FEV<sub>1</sub>, FEV<sub>1</sub>%, %FEV<sub>1</sub>, and MMF. The prediction equation of FEV<sub>1</sub> had coefficients of determination for age, height, and EM score. The estimated coefficient values of age and height in the present study were nearly equal to the values calculated using the prediction equations of the JRS. The usefulness of the HRCT findings of emphysema in COPD patients has previously been reported with regard to pulmonary function impairment<sup>23–26</sup>. This was the motivation behind our present ICOERD studies, as well as the study by Meijer *et al*<sup>5</sup>). Furthermore, the ICOERD assessment of EM may reflect obstructive ventilatory function indices (i.e. FEV<sub>1</sub>, FEV<sub>1</sub>%, and %FEV<sub>1</sub>). Therefore, the ICOERD can be quite accurate at describing respiratory diseases with EM.

### Conclusion

The results of the present study support the notation of ICOERD, as it correlates well with VFT, indicating it is adequate for the determination of EM. The results of the two assessment methods correlate well with each other, which

suggests that the ICOERD may be appropriately used internationally for epidemiological and clinical research studies. Further research studies recruiting patients with more severe pneumoconiosis cases are required to evaluate associations between RO/IR and ventilatory function.

### Acknowledgement

The grant sponsor of this study was the Ministry of Education, Culture, Sports, Science and Technology, Japan. The grant number is Grant-in-Aid for Scientific Research (B) (2) 13897004.

### References

- 1) Kusaka Y, Hering KG, Parker JE (2005) International Classification of HRCT for Occupational and Environmental Respiratory Diseases. Springer, Tokyo.
- 2) Tamura T, Suganuma N, Hering KG, Vehmas T, Itoh H, Akira M, Takashima Y, Hirano H, Kusaka Y (2014) Relationships (I) of international classification of high-resolution computed tomography for occupational and environmental respiratory diseases to ILO International classification of radiographs of pneumoconiosis for parenchymal abnormalities. Ind Health (submitted).
- 3) Suganuma N, Kusaka Y, Hering KG, Vehmas T, Kraus T, Parker JE, Shida H, International CT Classification Study Group (2006) Selection of reference films based on reliability assessment of a classification of high-resolution



- computed tomography for pneumoconioses. *Int Arch Occup Environ Health* **79**, 472–6.
- 4) Suganuma N, Kusaka Y, Hering KG, Vehmas T, Kraus T, Arakawa H, Parker JE, Kivisaari L, Letourneux M, Gevenois PA, Tuengerthal S, Crane MD, Shida H, Akira M, Henry DA, Nakajima Y, Hiraga Y, Itoh H, Hosoda Y (2009) Reliability of the proposed international classification of high-resolution computed tomography for occupational and environmental respiratory diseases. *J Occup Health* **51**, 210–22.
  - 5) Meijer E, Tjoe Nij E, Kraus T, van der Zee JS, van Delden O, van Leeuwen M, Lammers JW, Heederik D (2011) Pneumoconiosis and emphysema in construction workers: results of HRCT and lung function findings. *Occup Environ Med* **68**, 542–6.
  - 6) Ochsmann E, Carl T, Brand P, Raithel HJ, Kraus T (2010) Inter-reader variability in chest radiography and HRCT for the early detection of asbestos-related lung and pleural abnormalities in a cohort of 636 asbestos-exposed subjects. *Int Arch Occup Environ Health* **83**, 39–46.
  - 7) Vierikko T, Järvenpää R, Toivio P, Uitti J, Oksa P, Lindholm T, Vehmas T (2010) Clinical and HRCT screening of heavily asbestos-exposed workers. *Int Arch Occup Environ Health* **83**, 47–54.
  - 8) Takashima Y, Suganuma N, Sakurazawa H, Itoh H, Hirano H, Shida H, Kusaka Y (2007) A flat-panel detector digital radiography and a storage phosphor computed radiography: screening for pneumoconioses. *J Occup Health* **49**, 39–45.
  - 9) Huuskonen O, Kivisaari L, Zitting A, Kaleva S, Vehmas T (2004) Emphysema findings associated with heavy asbestos-exposure in high resolution computed tomography of Finnish construction workers. *J Occup Health* **46**, 266–71.
  - 10) Bergin CJ, Müller NL, Vedal S, Chan-Yeung M (1986) CT in silicosis: correlation with plain films and pulmonary function tests. *AJR Am J Roentgenol* **146**, 477–83.
  - 11) Oksa P, Suoranta H, Koskinen H, Zitting A, Nordman H (1994) High-resolution computed tomography in the early detection of asbestosis. *Int Arch Occup Environ Health* **65**, 299–304.
  - 12) Piirilä P, Kivisaari L, Huuskonen O, Kaleva S, Sovijärvi A, Vehmas T (2009) Association of findings in flow-volume spirometry with high-resolution computed tomography signs in asbestos-exposed male workers. *Clin Physiol Funct Imaging* **29**, 1–9.
  - 13) Piirilä P, Lindqvist M, Huuskonen O, Kaleva S, Koskinen H, Lehtola H, Vehmas T, Kivisaari L, Sovijärvi AR (2005) Impairment of lung function in asbestos-exposed workers in relation to high-resolution computed tomography. *Scand J Work Environ Health* **31**, 44–51.
  - 14) Vehmas T, Oksa P, Kivisaari L (2012) Lung and pleural CT signs predict deaths: 10-year follow-up after lung cancer screening of asbestos-exposed workers. *Int Arch Occup Environ Health* **85**, 207–13.
  - 15) Akgun M, Araz O, Akkurt I, Eroglu A, Alper F, Saglam L, Mirici A, Gorguner M, Nemery B (2008) An epidemic of silicosis among former denim sandblasters. *Eur Respir J* **32**, 1295–303.
  - 16) Ooi GC, Tsang KW, Cheung TF, Khong PL, Ho IW, Ip MS, Tam CM, Ngan H, Lam WK, Chan FL, Chan-Yeung M (2003) Silicosis in 76 men: qualitative and quantitative CT evaluation—clinical-radiologic correlation study. *Radiology* **228**, 816–25.
  - 17) Japan Industrial Safety and Health Association (1991) Industrial safety and health law and related legislation of Japan. Japan Industrial Safety and Health Association, Tokyo.
  - 18) Global initiative for chronic obstructive lung disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. <http://www.goldcopd.org/>. Accessed November 19, 2014.
  - 19) Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, ATS/ERS Task Force (2005) Standardisation of spirometry. *Eur Respir J* **26**, 319–38.
  - 20) Baldwin ED, Cournand A, Richards DW Jr (1948) Pulmonary insufficiency; physiological classification, clinical methods of analysis, standard values in normal subjects. *Medicine (Baltimore)* **27**, 243–78.
  - 21) The Committee of Pulmonary Physiology Japanese Respiratory Society (2004) Guidelines for pulmonary function tests: spirometry, flow-volume curve, diffusion capacity of the lung. Japanese Respiratory Society, Tokyo.
  - 22) Bégin R, Bergeron D, Samson L, Boctor M, Cantin A (1987) CT assessment of silicosis in exposed workers. *AJR Am J Roentgenol* **148**, 509–14.
  - 23) Gupta PP, Yadav R, Verma M, Agarwal D, Kumar M (2008) Correlation between high-resolution computed tomography features and patients' characteristics in chronic obstructive pulmonary disease. *Ann Thorac Med* **3**, 87–93.
  - 24) Park KJ, Bergin CJ, Clausen JL (1999) Quantitation of emphysema with three-dimensional CT densitometry: comparison with two-dimensional analysis, visual emphysema scores, and pulmonary function test results. *Radiology* **211**, 541–7.
  - 25) Akira M, Toyokawa K, Inoue Y, Arai T (2009) Quantitative CT in chronic obstructive pulmonary disease: inspiratory and expiratory assessment. *AJR Am J Roentgenol* **192**, 267–72.
  - 26) Diaz AA, Bartholmai B, San José Estépar R, Ross J, Matsuoka S, Yamashiro T, Hatabu H, Reilly JJ, Silverman EK, Washko GR (2010) Relationship of emphysema and airway disease assessed by CT to exercise capacity in COPD. *Respir Med* **104**, 1145–51.