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A Method for Visual Scoring of Pulmonary Mycobacterium Avium Complex Disease: "NICE Scoring System"

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Abstract

Recently, increase of non-HIV nontuberculous lung disease has been noticed but the chemotherapy of this disease is prolonged because no bactericidal drugs are available. To correctively evaluate the course of disease, X-ray images have been the most reliable method. Yet a quantitative assessment has not been established.

Method: Image of *M. avium* complex lung disease (MAC) is composed of nodule, infiltration (consolidation), cavity and bronchiectasis. We assess the occupied area of each factor on 6-divided lung field, and constructed a system named "NICE scoring system" on PC that makes it possible to easily score in actual practice.

Results: This method is well performed for chest radiography (CXR) images and also CT images. Validation tests of intra rater, inter rater and scoring for identical case by CXR images versus CT images show moderate to substantial kappa statistics and significant correlations.

Conclusion: This method is useful to evaluate the radiographic image of MAC lung disease.

Keywords: Nontuberculous lung disease; *M. avium*; Chemotherapy; Virulent bacterium

Introduction

In recent years there has been an increase in the incidence of nontuberculous mycobacteriosis, particularly of *Mycobacterium avium* complex lung disease, among people without HIV infection in many countries [1]. In Japan, the estimated incidence rate of nontuberculous mycobacteriosis in the 1970s was around 1.0 per 100,000 populations, but by 2007 it had risen to about 5.8 per 100,000, the highest level in the world [2]. No bactericidal drug or protocol of combination drugs has yet been found for nontuberculous mycobacteriosis [3],

Therefore long-term multidrug therapy with rifampicin (RFP), ethambutol (EB), and clarithromycin (CAM) has become the standard treatment based on numerous clinical experiences [1].

In contrast to chemotherapy for tuberculosis, the initial achievement of conversion to culture-negative does not mean a cure, because bacteriological relapse, recurrence of the clinical manifestations and imaging findings are considerably common after the first treatment [4]. *Mycobacterium tuberculosis* is a strongly virulent bacterium for human tissue. Therefore slight existence of tuberculous bacilli forms new lesions certainly. However, nontuberculous mycobacteria have weak virulence generally and often make no new lesion with long lasting colonizing state [5]. They make less inflammation than tuberculous bacilli and sometimes produce little amount of sputum. Although detection of bacteria in sputum is required to make the diagnosis [6], it is inadequate as a method of assessing the clinical course of the MAC infection, because quantitative evaluation is difficult with sputum specimens. However, X-ray images are reliably available at the time required, and reflect the degree of destruction of the lung parenchyma by disease with more precision.

Consequently, there has been a need for indices that would make it possible to accurately evaluate the efficacy of chemotherapy and changes in the patient's condition.

No biomarkers have been established for monitoring the course of nontuberculous mycobacteriosis, and Chest X-ray Radiography (CXR) or Computed Tomography (CT) findings have been used as the most sensitive and reliable objective indices. However, no sufficiently practical method of quantitatively assessing the CXR images has been established. We devised and named the "NICE (nodule, infiltration or consolidation, cavity, ectasis) scoring system" mainly for CXR images of *Mycobacterium Avium* Complex (MAC) lung disease.

The aim of the present study was to design a practical and reliable semi-quantitative scoring system for the *Mycobacterium Avium* Complex (MAC) lung disease to assess the clinical course of infection. The "NICE (nodule, infiltration or consolidation, cavity, ectasis) scoring system" is also computer software that enables us to calculate the scoring and collect the data more easily.

Materials and Methods

This study depends upon the patients group of HIV-negative pulmonary MAC infection who fulfilled the diagnostic criteria of American Thoracic Society and Infectious Disease Society of America 2007, who visited to Fukujuji Hospital since January 2000 through February 2012. We selected randomly from these patients, 126 pairs of CT examination and plain chest X-ray examination within 3 months

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interval each other for the source of development and validation of this system.

CT studies were performed using a SOMATOM Sensation 16 (Siemens, Erlangen, Germany). The parameters used for evaluation were as follows: 5.0-mm section thickness at 5.0-mm intervals with a 512×512 reconstruction matrix; 140 kV and 146 mA (135-195 mA); scan pitch, 1.25; rotation time, 0.5 s; and a high-spatial-frequency algorithm. All images were obtained at window settings appropriate for lung parenchyma (level, -450 Hounsfield units [HU]; width, 1700 HU).

The components of MAC pulmonary disease radiography could simplify 4 categories. First, there are nodules (N) appearing as round, irregular, or branching shadows measuring <1 cm in diameter (Figure 1). Second, there are infiltrations (consolidations; I) seen as homogeneous shadows of unspecified shape measuring ≥ 1 cm in diameter. Third, cavities are shown as annular shadows ≥ 1 mm thick, which is not cystic bronchiectasis.

Finally, there is evidence of ectasia (E) identified by tramline shadows, and evidence of bronchial wall thickening, indicating bronchiectasis. The lungs were separated into six zones to assign each lesion to a specific position: the right and left upper zones delimited by the carina, the right and left middle zone between the carina and the lower pulmonary vein, and the right and left lower zones (Figure 2). Dividing each lung field into 3 zones has been the traditional method, which is used in the International Labor Organization (ILO) classification to classify the CXR images of pneumoconiosis patients [7].

Furthermore we added lung field addressing, the upper zone, middle zone, and lower zone of the right lung field are recorded as "1", "3", and "5", respectively, in the patient's chart, and the corresponding zones of the left lung field as "2", "4", and "6", respectively. Addressing the lung field enables us to recognize the position of lesion also by the character information alone and is useful for extracting the specific lesions from the cumulated data. The percentage of the area of each zone that is occupied by each of the findings (N, I, C, and E) is scored as follows:

0: 0%

1: More than 0% but less than 25%

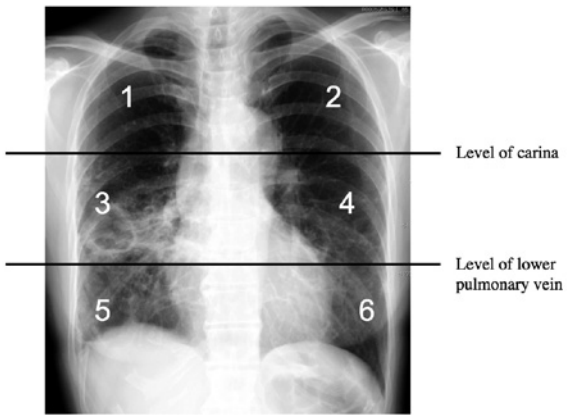

Figure 1: A horizontal line passing the tracheal bifurcation bounds the upper and middle lung fields. Similarly, a horizontal line passing through the lower pulmonary vein separates the middle and lower lung fields. In total, both lung fields are divided into 6 zones, each zone is addressed as 1 to 6.

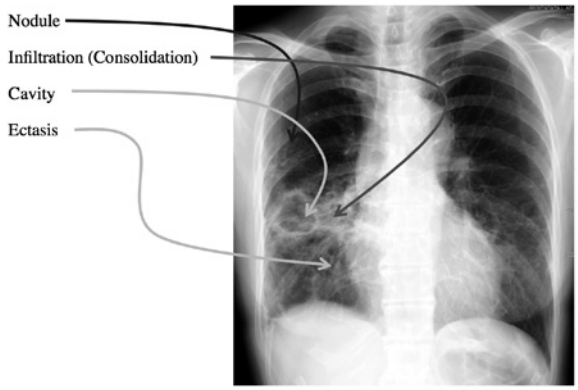

Figure 2: Pulmonary MAC image is composed mainly from four factors. Nodule (N) is essentially round shape within 1 cm in diameter. Infiltration (I) is seen as homogeneous shadow over 1cm in diameter. Cavity (C) is an annular shadow with over 1mm wall thickness. Tramline or bronchial wall thickening indicates Ectasis (E).

2: 25% or more but less than 50%

3: 50% or more but less than 75%

4: 75% or more

According to the calculations described above, total scores range from 0 to 96. This semi-quantitative scoring system for MAC lung disease images is designed to evaluate the CXR primarily, but can be applied to chest CT images. As shown in (Figure 2), we constructed a system that makes it possible to accumulate data in various ways by using personal computers (PC) or optical mark reader (OMR) sheets, because what is most important in actual practice is how easily the scoring can be completed. After ten-hours training under the advisory radiologist, two pulmonary physicians with over 15 years' clinical experience read and scored discretely the images of CXR and CT.

We evaluate this scoring method about 1) intra-rater variability 2) inter-rater variability 3) CXR vs. CT images. Statistical calculations of weighted kappa statistics for categorical variables were performed using STATA 12 (Stata corp LP, College Station, TX, USA). Non-parametric Spearman's Rank correlations and Wilcoxon matched-pairs signed rank tests were by GraphPad Prism6 (GraphPad, La Jolla, California, USA).

We adopted the following guidelines for interpretation of Kappa coefficients: <0, poor agreement; 0-0.20, slight; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, substantial; and 0.81-1.00, almost perfect [8].

The ethics committee of the Fukujuji Hospital approved the study protocol as a retrospective observational radiological analysis, August 2012.

Results

The NICE scoring system was tested for intra-rater and inter-rater agreement using CXR images (N=57, N=63) from patients with MAC lung disease. Kappa values about each four factors appeared as moderate to substantial level agreements. N and E factors show relatively low-grade values (Table 1). The correlation analysis of total score by Spearman's rank-test showed significantly high r values (Figure 3).

Although, NICE scoring system has been devised mainly targeting plain CXR images, we attempted CT images evaluation and kappa coefficients revealed relatively high scores (Table 1 and Figure 4).

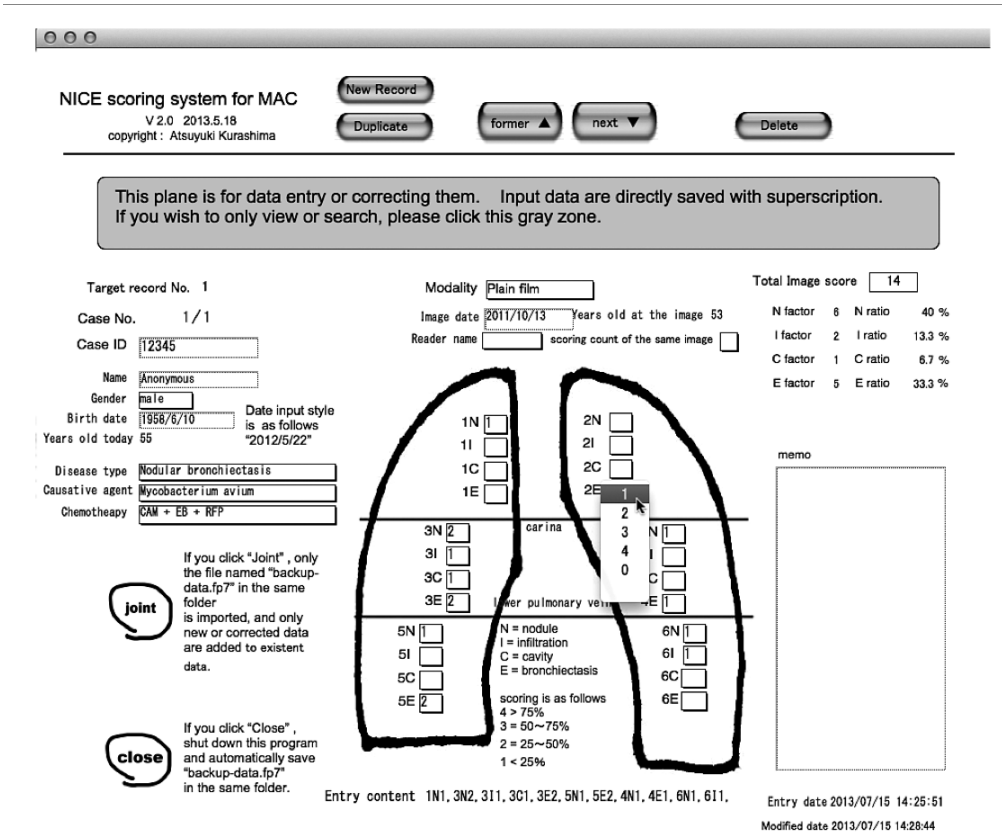

Figure 3: NICE scoring system for MAC lung disease on the PC software. Scoring numbers are selected from the popup menu and the results of each "NICE" factor and each "NICE" ratio are displayed immediately with real time calculation.

Same cases scoring with 1st vs. 2nd (N=57)	**Weighted kappa**	**95% confidence interval**	**p value**
N	0.5294	0.4372-0.6215	0.0000
I	0.6741	0.5410-0.8073	0.0000
C	0.6370	0.4752-0.7988	0.0000
E	0.5567	0.4737-0.6398	0.0000
Same cases scoring with A rater vs. B rater (N=63)	**Weighted kappa**	**95% confidence interval**	**p value**
N	0.6029	0.5385-0.6673	0.0000
I	0.6108	0.4496-0.7219	0.0000
C	0.6134	0.4226-0.8041	0.0000
E	0.5319	0.4457-0.6180	0.0000
Same cases scoring with CR vs. CT (N=61)	**Weighted kappa**	**95% confidence interval**	**p value**
N	0.6568	0.5911-0.7224	0.0000
I	0.6831	0.6056-0.7605	0.0000
C	0.5702	0.3873-0.7531	0.0000
E	0.6611	0.5876-0.7346	0.0000

Table 1: Weighted kappa coefficients of each N, I, C, E factor by intra-rater, inter-rater and CXR versus CT scorings show moderate to substantial level agreement. In the C and I factors of CXR with each other, the relatively high kappa values are seen, whereas in the case of CXR versus CT, the C factors show relatively low value.

We evaluated the NICE scores for the 72 cases MAC lung disease longitudinal CXR images of pre-standard chemotherapy including rifampicin, ethambtol and clarithromycin that lasted over six month and post the treatment status. Total score including N factor and I factor significantly decreased after standard chemotherapy for MAC lung disease (Figure 5), but the scores of C factor and E factor present no significant decrease.

Altogether, these data demonstrate that the semi-quantitative scoring system we developed is significantly reliable and useful for practical purposes.

Discussion

For patients with MAC lung disease, it is essential to monitor treatment responses due to the high incidence of bacteriological relapse and recurrence of the clinical manifestations.

Unfortunately, there is no classification of disease severity in the area of MAC lung disease. In the tuberculous lung disease, the classification of chest X-ray image proposed by the National Tuberculosis Association of the U.S.A in 1950 was simple and at one time that was widely used, but it was rescinded in 1974 [9]. For a long time thereafter no classification was ever adopted worldwide.

However, several attempts at radiographic classification have been proposed since the introduction of CT into clinical practice.

Casarini M proposed for pulmonary tuberculosis [10], dividing each lung field on high-resolution computed tomography (HRCT) images into 3 zones and scoring each zone for extent of seven findings, including "miliary nodules". Scores of 1 to 4 are assigned based on the percentage of the area of each zone occupied by the finding i.e., <25%, 25-50%, 50-75%, >75%.

Ors F and others assessed a similar method [11] and reported

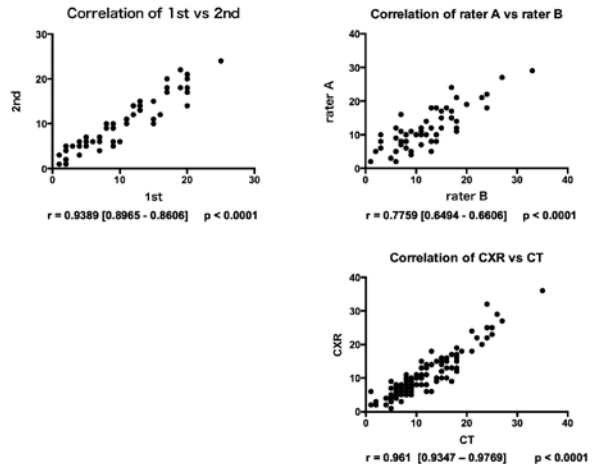

Figure 4: In all three comparisons, high correlations of total scores by Spearman's rank-test are demonstrated. Correlation of CT versus CXR shows more narrow scatter range than that of CXR together.

pre and post standard chemotherapy (N = 72)	Wilcoxon matched-pairs signed rank test
N factor	<0.0001
I factor	<0.0001
C factor	0.0693
E factor	0.0582
Total score	<0.0001

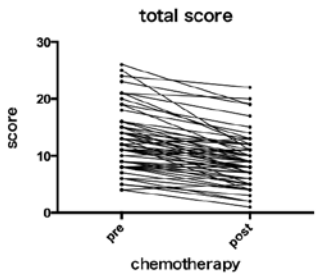

Figure 5: Differences between the scores of pre-chemotherapy and post–chemotherapy (479.1 mean days) were evaluated by Wilcoxon matched pairs signed rank test.
N factor, I factor and total score showed significant decreases, however, C factor and E factor do not present the same tendency.

that the total scores were strongly correlated with the numbers of tuberculous bacteria in sputum smears.

Moore EH has reported a method of evaluating images of the lungs of nontuberculous mycobacteriosis patients [12] in which each lung field is divided into a total of 10 zones along the anatomical divisions between the pulmonary lobes and in which the findings such as "bronchiectasis" in each zone are rated on a 3-grade scale according to the extent of their distribution.

Kitada et al. has devised a method [13] in which a total of 18 anatomical segments in both lungs is identified by conventional CT and the scores are expressed according to the number of segments that present seven category findings, for example, "small nodular" etc.

Song JW approached the HRCT scoring system modifying Bhalla's system for cystic fibrosis [14] to MAC lung disease [15]. This system is composed 9 assessment findings, for example, bronchiectasis, bronchiolitis, cavity etc. About each finding, severity and extent are judged by 4 grades. The extent is expressed how many segments have lesions. These methods devised by Moore, Kitada and Song for evaluation of the lungs of patients with nontuberculous myocobacteriosis are accurate in principle and enable detailed scoring of the findings, but it is very difficult to rapidly score large numbers of cases by their methods in clinical situations.

We present a new semi-quantitative scoring system for the identification and assessment of patients with MAC lung disease. This method mainly targets plain CXR images and as it does not require identification of anatomical segments, it can quickly assess the score of CXR images.

In the field of tuberculosis CXR image evaluation, more factors are required. Graham S reported the intra and inter reader agreements on the 1715 chest films with five broad categories for example multiple nodules, pleural disease, parenchymal infiltrates etc. [16]. These kappa scores were moderate to substantial. Zellweger J-R assessed 377 active TB CXRs in a similar way and showed kappa scores with 0.55 to 0.80 (two best readers) [17].

Ralf AP conducted a numerical score for grading CXR severity in pulmonary tuberculosis.

They evaluate the presence of nodules, consolidation, cavitation, bronchial lesions and fibrosis with the extent of opacification for three zones in each lung. Intra rater agreement showed slight to substantial results [18].

The results of our study are good at the level of comparable to above-described studies.

The kappa statistics of CT versus CXR show unexpectedly high correlations and the 95% intervals are narrower than the comparisons between CXR images. It is probable that in the case of CT versus CXR, the variation of rating is focused one way with a robustness of CT finding. Therefore this method is easily applied moreover for CT images with a certain level of reliability.

From these viewpoints, the "NICE scoring system" is as a useful and practical method applicable to both CXR and CT images. In our method, the total score and the ratio of each factor is represented in real time on the spot. Quick response of the process plays an important role in improving efficiency and motivation of the researchers.

Using this system, we evaluated the radiographic changes for MAC lung disease of 72 cases that treated with standard chemotherapy of 479.1 days on average. In our results, the standard chemotherapy showed a superiority effect on infiltrations and nodules, but the improvement was not seen for cavity or bronchiectasis in the evaluation period.

We have a few papers that have focused radiographic elemental changes after chemotherapy for MAC lung disease. Kuroishi et al. reported about 23 patient's CT findings treated with clarithromycin-contained regimen, improvements of nodules were higher than those of bronchiectasis and pleural thickening on follow up examinations [19]. These observations are consistent with our results.

Such a scoring system may facilitate objective evaluation of existing and newly developed therapeutic regimens. There are limitations in our study. We count N, I, C, E each factor with equal weight, but it should be assessed with more proper weight concerning the disease severity and it's prognosis. We consider it necessary to search for the

most appropriate weight for each factor. In the future, these tasks will be automatically and completely quantified in volume rendering method on the CT.

Conclusion

The "NICE scoring system" is a useful tool to assess the extent and contents of MAC lung disease with radiography.

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