Clinical Usefulness of HRCT in Assessing the Severity of Pneumocystis jirovecii Pneumonia

A Cross-sectional Study

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Abstract: The aim of this study was to investigate the clinical relevance of thoracic high-resolution computed tomography (HRCT) in evaluating the severity and outcome of Pneumocystis jirovecii pneumonia (PJP) in non-AIDS immunocompromised patients. We measured mean lung attenuation (MLA) and extent of increased attenuation (EIA) of PJP lesions on thoracic HRCT in 40 non-AIDS immunocompromised patients with PJP diagnosed by demonstration of the pathogens in cytological smears of bronchoalveolar lavage fluid. The MLA and EIA of PJP lesions on thoracic HRCT were used to investigate the severity of PJP. Clinically, the severity of PJP was determined by arterial oxygen tension/fraction of inspired oxygen concentration (PaO2/FiO2) ratio, acute physiology and chronic health evaluation (APACHE) II score, the need of mechanical ventilation, and death.

MLA highly correlated with EIA of PJP lesions ($\rho = 0.906$, $P < 0.001$). MLA and EIA of PJP lesions significantly correlated with PaO2/FiO2 ($\rho = -0.481$ and $-0.370$, respectively and $P = 0.007$ and 0.044, respectively). When intensive care unit (ICU) admission and HRCT performed were within 2 days, MLA and EIA of PJP lesions were significantly correlated with APACHE II score ($\rho = 0.791$ and 0.679, respectively and $P = 0.001$ and 0.009, respectively). There were significant differences in the values of MLA and EIA of PJP lesions between patients with and without assisted mechanical ventilator (MLA, median and [interquartile range, IQR, 25%, 75%] $572.10,[-572.10, -357.34]$ vs $-649.27$ $[-715.62, -594.01]$), MLA and EIA, median and [IQR 25%, 75%]$ 0.75 [0.66, 0.82]$ vs $0.53 [0.45, 0.68]$, $P = 0.003$, respectively). The data of MLA and EIA of PJP lesions had limited value in identifying survivors and non-survivors.

The MLA and EIA values of PJP lesions measured on thoracic HRCT might be valuable in assessing the severity of PJP in non-AIDS immunocompromised patients, but might have limited value in predicting the mortality of the patients.

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Abbreviations: AIDS = acquired immunodeficiency syndrome, APACHE = acute physiology and chronic health evaluation, BAL = bronchoalveolar lavage, BALF = bronchoalveolar lavage fluid, CXR = chest radiograph, EIA = extent of increased attenuation, FiO2 = inspired oxygen fraction, GGO = ground glass opacity, HRCT = high resolution computed tomography, HU = Hounsfield unit, IL = interleukin, KL-6 = Krebs von den Lungen-6, MCP = monocyte chemoattractant protein, MLA = mean lung attenuation, PaO2 = arterial oxygen tension, PaO2/FiO2 ratio = oxygenation index, PI = Pneumocystis jiroveci, PJP = Pneumocystis jirovecii, pneumonia, SD = standard deviation, SP-D = surfactant protein D, TGF = transforming growth factor, TNF = tumor necrosis factor.

INTRODUCTION

Pneumonia is one of the most common infections in immunocompromised patients.1 Pneumocystis jirovecii pneumonia (PJP) is a common and life-threatening infection in immunocompromised patients with or without acquired immuno-deficiency syndrome (AIDS).2 The non-AIDS immunocompromised group included patients with hematological malignancy, those with solid cancer, those undergoing solid organ, stem cell, or bone marrow transplantation, and those with connective tissue diseases or inflammatory disorders treated with long-term immunosuppressants. The clinical features of PJP can vary widely between patients with and without AIDS. PJP in non-AIDS patients present with more acute onset of symptoms, more severe hypoxemia and fare higher mortality.3–6 Without timely diagnosis and early institution of targeted treatment of trimethoprim-sulfamethoxazole or second-line agents including pentamidine, primaquine plus clindamycin, and atovaquone, patients rapidly progress to acute respiratory failure and are associated with high mortality. Because Pneumocystis jirovecii (PJ) cannot be cultured nowadays, the diagnosis depends on microscopic examination of sputum, bronchoalveolar lavage fluid (BALF), or lung tissue samples. The lower burden of PJ in patients without AIDS causes difficulty in detecting the organisms from the induced sputum and BALF samples.7,8

High-resolution computed tomography (HRCT) of the chest is an essential part of diagnostic evaluation for interstitial lung diseases or diffuse parenchymal lung diseases, and its use has a major impact on the utility of other diagnostic tests,
especially bronchoalveolar lavage (BAL) and surgical biopsy procedures. Thus, thoracic HRCT is helpful for early diagnosis and timely treatment of PJP. However, the patterns of PJP lesions shown on HRCT are reported to be different between the patients with and without AIDS. PJP in AIDS patients presents predominantly diffuse ground glass opacity (GGO), whereas a variety of patterns are reported in PJP of non-AIDS patients.4,9

The major thoracic HRCT findings of PJP included GGO, consolidation, nodules, cysts, pneumothorax, reticulation, and septal thickening.10–14 One characteristic feature is that the lesions of GGO and consolidation occupy diffusely in the lungs. The lesions of PJP increase attenuation except for cyst formation and pneumothorax. Furthermore, when PJP became more severe, GGO lesions might expand and/or progress to consolidation lesions.10–14

To our knowledge, the image studies on the clinical relevance of density and extent of pneumonia lesions in pneumonia severity and outcome of the patients have been very limited. Wilhelm et al15 investigated the severity of community-acquired pneumonia with chest radiograph (CXR), and the results indicated that non-survived patients had a significantly higher extent of infiltrates, increased density of infiltrates, and radiographic spread within 48 to 75 hours of admission. Persistent or progressive density of infiltrates was reported to be the independent factor for the mortality of the patients with community acquired pneumonia.

Currently, the role of HRCT in PJP is focused on the diagnosis. HRCT is more accurate than CXR in making a diagnosis of PJP.11,16 In addition, HRCT may be of value in detecting PJP when CXR is inconclusive in the setting of high index of clinical suspicion.12,17,18 To our knowledge, the studies on thoracic HRCT in evaluating the severity of PJP and in predicting outcome of the patients are limited. Some previous studies failed to show clinical relevance of image findings of PJP shown on HRCT.4,9

In this study, we measured mean lung attenuation (MLA) and extent of increased attenuation (EIA) of PJP lesions in both lungs shown on HRCT and explored their clinical relevance in the non-AIDS PJP patients.

PATIENTS AND METHODS

Non-AIDS PJP Patients

Forty consecutive non-AIDS immunocompromised patients with PJP diagnosed by identification of PJ cysts or trophozoites in BALF cytological smears at Taipei Veterans General Hospital from January 1, 2005 to June 30, 2013. The patients who were not subjected to thoracic HRCT or with concurrent other pulmonary infections were excluded. The institutional Review Board of Taipei Veterans General Hospital approved the study (IRB No.: 2010090191C and IRB No.: 96–04–02A), and written informed consents were obtained from all patients before entering the study of cytokines and inflammatory biomarkers in BALF. The clinical data of some patients were published previously.19,22 The cases enrolled in this study were determined by the study period approved by the IRB of Taipei Veterans General Hospital, diagnostic criteria of PJP used in this study and written informed consents of the patients.

Oxygenation Index

The arterial oxygen tension (PaO₂) was analyzed with ABL III (Radiometer, Copenhagen, Denmark). Oxygenation index (PaO₂/FiO₂ ratio) was calculated as PaO₂ divided by inspired oxygen fraction (FiO₂).

BALF Samples

The fiberoptic bronchoscope (Model BF20 or P20; Olympus, Tokyo, Japan) was wedged in the orifice of a lobar or segmental bronchus of right middle lobe or lingular division or other appropriate location. Diagnostic BAL was done using 3 aliquots of a 50-ml sterile isotonic sodium chloride. Aspirates were pooled into a siliconized container and kept on ice during transport. Part of the retrieved BALF was subjected to Papanicolaou and Riu’s staining routinely. Some slides were stored for subsequent special staining if clinically indicated.

Control Group

To compare the effect of diffuse air space lesions on HRCT on MLA and EIA in PJP, normal lungs were used as control. Ten subjects without abnormal findings on thoracic HRCT and pulmonary function testing were included as the control group: sarcoidosis in 4 and uveitis in 6 patients.

Thoracic HRCT

A total of 40 HRCT were performed with two types of CT scanners, Aquilion 64, Toshiba Medical Systems, Otawara, Japan, or Somatom Sensation 16, Siemens Medical Solutions, Erlangen, Germany. Patients were scanned in the supine position at the suspended end-inspiratory volume. Scans were obtained using 1-mm collimation at 10-mm intervals, extending from the lung apices to below the costophrenic angles. The tube voltage was 120 to 130 KV, and the tube current-time was 120 to 300 mAs based on patient’s body building. The routine protocol of CT scan of the chest at Taipei Veterans General hospital is 5-mm slice thickness if HRCT is not indicated. The whole CT procedure was performed without the use of contrast medium. All images were obtained at window levels appropriate for lung parenchyma (window width 1600 Hounsfield units [HU], window level -600 HU). A 35 45-cm fields of view and a 512 × 512 reconstruction matrix were used. Patient images were reconstructed with a high-spatial-frequency algorithm for lung parenchymal analysis. The image review was performed on PACS stations.

Image Analysis

The method of image analysis was modified from Best et al.20 Nearly all slices of HRCT were included except for 1 to 2 slices at bilateral basal regions containing significant amount of diaphragm. Both lung fields on each slice were outlined manually for 3 times, excluding the central great vessels, bronchi, and mediastinum. The attenuation was expressed by HU and the segmented lungs were analyzed with free image analysis software, ImageJ (US National Institutes of Health, Bethesda, MD). It could count the pixel numbers of each HU value within regions of interest, and also the mean HU values. The MLA was determined by summation of HU values of every pixel within regions of interest in all slices divided by total pixel numbers of the lungs. The EIA was calculated as the number of pixels with attenuation >−750 HU divided by total pixel numbers. The values of −750 HU were used as the lower threshold of GGO in this study were based on previous reports21–23 and our clinical experience, although the lower threshold of GGO has not yet been well defined. The mean values of the 3 MLA and EIA values measured were used for analysis. The HRCT scans were
independently interpreted by 1 experienced thoracic radiologists (W-HY) and 1 chest physician (C-WC), and in case of disagreement, the decisions were made by consensus.

**Measurement of Cytokines and Biomarkers**

The levels of cytokines in the supernatants of BALF were measured by the commercially available enzyme-linked immunosorbent assay kits including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-8, monocyte chemoattractant protein (MCP)-1, IL-10, and transforming growth factor (TGF)-β1 (R&D Systems; Minneapolis, MN). The levels of biomarkers in the supernatants of BALF were determined by commercial enzyme-linked immunosorbent assay kits according to the manufacturer’s instructions including Krebs von den Lungen-6 (KL-6, Eisai, Tokyo, Japan) and surfactant protein D (SP-D, Biovendor, Modrice, Czech Republic), respectively. The lower limits of these variables were adapted as follows: IL-1β, 1 pg/mL; TNF-α, 4.4 pg/mL; IL-8, 3.5 pg/mL; MCP-1, 5.0 pg/mL; IL-10, 3.9 pg/mL; TGF-β1, 4.61 pg/mL; SP-D, 0.2 ng/mL; and KL-6, 201 U/mL.

**Statistical Analysis**

Data were expressed as mean and standard deviation (SD). Nonparametric tests were used to analyze the variables because most of them were not normally distributed. The correlations between variables were determined by Spearman rank correlation coefficients. Comparisons of variables between PJP patients and normal lung controls were made using Mann–Whitney U test. Comparisons of the variables in PJP patients who were subdivided into 2 groups based on the variables including the use of mechanical ventilator or survivor status were made using the Mann–Whitney U test. Significance was defined as \( P < 0.05 \). Statistical analysis was performed using SPSS version 13 (SPSS, Chicago, IL).

**RESULTS**

**Demographic and Clinical Features of Non-AIDS Patients with PJP**

The demographic characteristics and clinical data of 40 non-AIDS patients with PJP are shown in Table 1. The most common category of immunosuppressed patients was organ transplants.

**Thoracic HRCT Findings**

GGO was seen in 85% (n = 34), consolidation in 77.5% (n = 31), reticular pattern in 45% (n = 18), septal thickening in 75% (n = 30), linear opacity in 85% (n = 34), bronchiectasis and/or bronchiolectasis in 15% (n = 6), small nodules in 10% (n = 4), few cysts formation in 20% (n = 8), small sized pleural effusion in 15% (n = 6), pneumomediastinum in 2.5% (n = 1) patients. GGO combined with consolidation was found in all patients (100%).

**MLA and EIA of HRCT in PJP Patients and Normal Lung Controls**

The MLA and EIA values in PJP patients expressed in median and (IQR, 25%, 75%) were -569.05 (-684.54, -485.62) and 0.68 (0.51, 0.77), respectively. The MLA and EIA data in normal lung controls expressed in median and (IQR, 25%, 75%) were -855.83 (-874.70, -818.06) and 0.12 (0.11, 0.19), respectively. The values of MLA and EIA were significantly higher in PJP patients than in normal lung controls \((P < 0.001)\) in PJP patients. Similarly, such correlation was observed in HRCT of the normal lung controls \((P = 0.909, P < 0.001)\).

**Correlations Between MLA and EIA**

The values of MLA were highly correlated with those of EIA \((\rho = 0.906, P < 0.001)\) in PJP patients. Similarly, such correlation was observed in HRCT of the normal lung controls \((\rho = 0.909, P < 0.001)\).

**Correlations Between MLA and EIA of PJP Lesions and Oxygenation Index**

Oxygenation index is defined as PaO2/FiO2 and usually used to assess the severity of lung injury. The correlations between the data of MLA and EIA of PJP lesions and oxygenation index in PJP patients were analyzed. Significant correlation was observed between the values of MLA of PJP lesions and oxygenation index \((\rho = -0.481, P = 0.007)\) and between the data of EIA of PJP lesions and oxygenation index \((\rho = -0.370, P = 0.044)\).

**Correlations Between MLA and EIA of PJP Lesions and APACHE II Score**

When the interval between ICU admission and thoracic HRCT performed was within 2 days, a significant correlation was observed between the values of MLA of PJP lesions and acute physiology and chronic health evaluation (APACHE) II score \((\rho = 0.791, P = 0.001)\). Significant correlation was also

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**TABLE 1. Demographic and Clinical Characteristics of 40 Patients With PJP**

| Sex (M/F) | 19/21 |
| Age, years | 48.0 ± 13.9 |
| Underlying diseases | |
| Hematological malignancy | 5 |
| s/p chemotherapy | 4 |
| Allogeneic peripheral blood stem cell transplantation | 6 |
| Connective tissue diseases | 6 |
| Glomerulonephritis with immunosuppressants | 4 |
| Prostate cancer with immunosuppressants | 1 |

| PaO2/FiO2, N = 29 | 230.00 (163.40, 293.33) |
| APACHE II score (N = 24) | 23 (18, 26.5) |
| Intervals between onset of PJP and thoracic HRCT, days | 5.00 (3.25, 9.00) |
| ICU admission, case number (%) | 24 (60.0) |
| Ventilator needed, case number (%) | 23 (57.5) |
| Death, case number (%) | 17 (42.5) |

| Data are expressed as case number and % in parenthesis. Age is expressed as mean ± SD. PaO2/FiO2, APACHE II score, intervals between onset of PJP and thoracic HRCT are expressed as median IQR (25%, 75%). APACHE = acute physiology and chronic health evaluation, FiO2 = fraction of inspired oxygen, HRCT = high-resolution computed tomography, ICU = intensive care unit, PaO2 = arterial arterial oxygen tension, PJP = *Pneumocystis jirovecii* pneumonia. |
noted between the data of EIA of PJP lesions and APACHE II score ($\rho = 0.670, P = 0.009$).

Comparisons of MLA and EIA of PJP Lesions Between the Patients Divided Into Groups by the Use of Mechanical Ventilator or Outcome

Compared with PJP patients without mechanical ventilator, the values of MLA and EIA were significantly higher in PJP patients with mechanical ventilator (Table 2). However, there were no significant differences in the data of MLA and EIA between the patients divided into survivors and nonsurvivors (Table 2).

Correlation Between BALF Levels of IL-8, Inflammatory Biomarkers, Pro-inflammatory/ Anti-inflammatory Cytokine Ratio, and MLA and EIA

The results are shown on Table 3. Significant correlation was observed between the values of IL-8 and MLA ($\rho = 0.40, P = 0.017$). The values of KL-6 correlated significantly with those of MLA and EIA, respectively ($\rho = 0.52, P = 0.002$ and $\rho = 0.44, P = 0.009$, respectively). The values of SP-D correlated significantly with those of MLA and EIA respectively ($\rho = 0.50, P = 0.002$ and $\rho = 0.45, P = 0.006$). Significant correlation was observed between IL-8/IL-10 ratio and the values of MLA ($\rho = 0.40, P = 0.019$). IL-8/TGF-β1 ratio correlated significantly with the data of MLA ($\rho = 0.39, P = 0.021$).

DISCUSSION

In the present study, we demonstrated that the mean density of lung parenchyma lesions was highly correlated with the lesion extent in PJP shown on thoracic HRCT. Our results indicated that the more extensive of the lesions the more dense of the lesions of PJP was found on HRCT in non-AIDS immunocompromised patients. Furthermore, we demonstrated that MLA and EIA of PJP lesions were correlated well with the indicators of clinical severity of PJP as evidenced by oxygenation index and APACHE II scores. It is well known that the lung injury of PJP is a result of host exuberant immune response to PJP rather than the injury caused by pathogen itself. Our previous and other studies indicated that an imbalance of pro-inflammatory and anti-inflammatory cytokines in BALF was found in PJP patients with and without AIDS. Some BALF pro-inflammatory/anti-inflammatory cytokine ratios were significantly higher in the patients requiring mechanical ventilation and in nonsurvivors.

Furthermore, our results indicated that IL-8/IL-10 ratio and IL-8/TGF-β1 ratio were highly correlated with MLA, and inflammatory biomarkers KL-6 and SP-D were significantly correlated with MLA and EIA of PJP lesions (Table 3). Taken together, these results could strongly support that the imaging findings of thoracic HRCT were highly correlated with clinical severity of PJP in non-AIDS immunocompromised patients and might be of considerable value in assessing the severity of PJP.

The studies on clinical relevance of thoracic HRCT in PJP of immunocompromised patients with or without AIDS are limited. Tokuda et al described 3 patterns of opacity on HRCT in PJP patients with rheumatoid arthritis and AIDS. However, they failed to find any significant correlation between HRCT patterns of opacity and clinical features including clinical signs, serum markers, ventilator usage and death. Tasaka et al used these HRCT patterns to evaluate PJP patients with malignancy and AIDS. In addition, they scored the extent of GGO and consolidation in relatively small regions in the lungs. The results indicated that no significant correlation was observed between HRCT findings and clinical parameters including oxygenation index, serum levels of immunoglobulin G, albumin, lactate dehydrogenase, C-reactive protein, and KL-6.

At variance with these 2 studies, our results showed that extent of GGO and consolidation of PJP were correlated well with clinical severity indicators including oxygenation index, APACHE II scores, and the use of mechanical ventilator. The discrepancies of the results between previous and our present studies may be explained in part by that previous studies sampled only near 10% of the lungs, which might cause significant sampling errors. Another reason might be that we pooled the results of GGO and consolidation lesions in both lungs for evaluation.

To our knowledge, there are no reliable indicators used to assess the severity of PJP and to predict the outcome of the patients with PJP. It is plausible that the density and extent of PJP lesions as shown on HRCT might reflect the severity of lung injury. This assumption was supported by the results of the present study as evidenced by that the density and extent of PJP lesions were highly correlated with the data of oxygenation index, APACHE II score, and the use of mechanical ventilator. It is well known that the lung injury of PJP is a result of host exuberant immune response to PJP rather than the injury caused by pathogen itself. Our previous and other studies indicated that an imbalance of pro-inflammatory and anti-inflammatory cytokines in BALF was found in PJP patients with and without AIDS. Some BALF pro-inflammatory/anti-inflammatory cytokine ratios were significantly higher in the patients requiring mechanical ventilation and in nonsurvivors. Furthermore, our results indicated that IL-8/IL-10 ratio and IL-8/TGF-β1 ratio were highly correlated with MLA, and inflammatory biomarkers KL-6 and SP-D were significantly correlated with MLA and EIA of PJP lesions (Table 3). Taken together, these results could strongly support that the imaging findings of thoracic HRCT were highly correlated with clinical severity of PJP in non-AIDS immunocompromised patients and might be of considerable value in assessing the severity of PJP.

### Table 2. Comparisons of MLA and EIA of PJP Lesions Between the Patients Divided Into Groups by the Use of Mechanical Ventilator or Outcome

|                        | Without Ventilator (N = 17) | With Ventilator (N = 23) | P       |
|------------------------|-----------------------------|--------------------------|---------|
| MLA                    | −649.27 (−715.62, −594.01) | −516.44 (−572.10, −375.34) | <0.001  |
| EIA                    | 0.53 (0.45, 0.68)          | 0.75 (0.66, 0.82)        | 0.003   |
| Survivor (N = 23)      |                             | Nonsurvivor (N = 17)     |         |
| MLA                    | −626.71 (−700.29, −500.26) | −525.76 (−609.79, −440.06) | 0.085   |
| EIA                    | 0.61 (0.48, 0.74)          | 0.73 (0.60, 0.81)        | 0.085   |

Data are expressed as median IQR (25%, 75%). MLA was expressed as Hounsfield unit (HU). EIA was calculated as the number of pixels with attenuation > −750 HU divided by total pixel numbers. EIA = extent of increased lung attenuation, MLA = mean lung attenuation, PJP = *Pneumocystis jirovecii* pneumonia.
Although MLA and EIA were shown to be significantly higher in patients with more severe PJP, however, we failed to show the usefulness of MLA and EIA of PJP lesions measured from thoracic HRCT in predicting mortality of PJP in non-AIDS immunocompromised patients. It is unclear whether thoracic HRCT could be of value in assessing the severity of PJP in non-AIDS immunocompromised patients but have limited value in predicting outcome of the patients. The discrepancies may be explained as follows. First, different time intervals were found between the onset of PJP and the date of HRCT performed among the patients studied. Second, PJP lesions shown on HRCT might progress before the administration of specific treatments for PJP. Vogel et al. showed that the lesions of PJP shown on HRCT became worse before specific therapy was given. Third, the causes and disorders of non-AIDS immunocompromised patients in our patients varied widely. Accordingly, the effects of immunosuppression status resulted from various causes and disorders and the use of immunosuppressive agents on the mortality of these patients could not be evaluated by thoracic HRCT alone. Finally, the use of steroid and timely adequate use of steroid treatment might explain in part. Further studies with larger populations are needed to verify these issues.

There are some limitations in this study. First, when cystic lesions of PJP on thoracic HRCT have substantial volume, the low attenuation of the cystic lesions may reduce the attenuation and confound the measuring mean lung density of PJP lesions. The cysts were small and found occasionally in our patients. Accordingly, the cystic lesions of PJP did not affect the results of the present study. Second, pneunothorax caused by PJP may confound the measurement of mean lung density. However, pneumothorax was not found in the present study. Third, unusual presentation of PJP including large nodules, masses, and massive pleural effusion may add challenge to the measurement of the density and extent of lung lesions. Because the aforementioned conditions were not found in our patients, the results of the present study might have considerable clinical relevance. Fourth, the results obtained from single medical center may not be generalized to other medical centers or hospitals. Further studies with larger populations are required to verify these issues.

In summary, our results suggested that measurements of MLA and EIA of PJP shown on thoracic HRCT might have considerable value in assessing the severity of PJP in non-AIDS immunocompromised patients. The findings are of clinical relevance because examination of thoracic HRCT is noninvasive and is usually done clinically in non-AIDS immunocompromised patients with chest radiographic findings highly suggestive of PJP. The role of thoracic HRCT in predicting outcome or mortality of non-AIDS immunocompromised patients needs further studies with larger populations to verify.

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