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Jiinshihoto may improve immunity by improving depression in patients with mild pulmonary Mycobacterium avium-intracellulare complex disease: a preliminary study

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Abstract

Background: In Japan, pulmonary *Mycobacterium avium-intracellulare* complex (MAC) disease is highly prevalent. This study aimed to evaluate the efficacy of Jiinshihoto (JST) for treating pulmonary MAC disease.

Methods: Twenty-four patients, not receiving standard treatment for pulmonary MAC disease, were enrolled in this study; of these, 21 patients (3 patients dropped out of the study) were eligible and selected to participate. They were administered JST (3.0 g; Tsumura Co., Tokyo, Japan) three times per day for 12 months. Their weight, chronic obstructive pulmonary disease assessment test (CAT) score, NK cell activity, chest computed tomography (CT) results, blood sample results, Self-rating Depression Scale (SDS) scores, and State-Trait Anxiety Inventory (STAI) scores were measured: (i) before JST administration, (ii) after 3 months, and (iii) at the end of the study.

Results: Before JST administration, the exacerbation group (n = 10 patients; 6 patients with worsened conditions at the end of the study and 4 patients who were switched to standard treatment during the study because of exacerbation) had a significantly low body mass index (BMI), mild depression, and high anxiety. The overall patient population showed no significant differences in the chronic obstructive pulmonary disease assessment score, body weight, or natural killer cell activity after 3 months of treatment; however, the SDS score improved significantly. At the end of treatment, the nutritional scores had worsened, but the SDS score improved significantly. Specifically, the SDS scores improved significantly only in the non-exacerbation group (n = 11 patients), and natural killer cell activity improved in the non-exacerbation group. Additionally, a comparison of the data of both groups before and after JST administration showed that the exacerbation group had significantly lower BMI and worse CT scores when using a BMI cutoff of 18.4 (sensitivity, 81.8%; specificity, 70%).

Conclusion: Patients with a high BMI and low CT score at the time of initial diagnosis may benefit from JST treatment, which may significantly improve depression and immunity and prevent disease progression. Therefore, JST may be an effective treatment in selected pulmonary MAC patients.

Trial registration: This study has been registered in the UMIN-Clinical Trials Registry (UMIN000033590, August 1, 2018).

1. Introduction

In Japan, in 2014, the estimated incidence of pulmonary nontuberculous mycobacteria (NTM) infection was 14.7 (per 100,000 population)—a more rapid increase (approximately 2.6 times) than that recorded in 2007; furthermore, pulmonary *Mycobacterium avium-intracellulare* complex (MAC) disease accounted for 88.8% of these infections (1). Few patients are diagnosed at the time of medical examination, and usually present without subjective symptoms or symptom exacerbation; however, others experience exacerbation and require treatment. Furthermore, many patients with MAC disease have neurosis and depression, but there has been no accurate assessment of these simultaneous conditions (2).

Kampo formulas, such as Hochuekkito, Juzentaihoto, and Ninjinyoeito are reported to demonstrate desirable treatment outcomes in NTM. Hochuekkito has been found to suppress the increasing number of bacteria discharged in sputum, prevent chest deterioration observed through imaging, and improve appetite (3). Hochuekkito also increases the population of natural killer (NK) cells (4); however, these aforementioned studies are older, and recent reports are scarce.

Jiinshihoto (JST; pronounced “ziyin-zhibao-tang” in Chinese) is a Kampo formula described in the Wanbinhuichun textbook (5) in the category of consumptive disease. JST is composed of crude drugs that aid in "moistening the lung", "clearing heat", and "relieving cough". It is suitable for patients—especially females, with chronic cough and sputum, qi stagnation, and other unidentified symptoms. It is considered an effective formula for chronic inflammatory diseases of the airways. In Japanese, “jiin” means “nourishing yin” or “tonifying yin”. Yin deficiency is a pathological change marked by diminished moistening, calming, and downbearing effects, and yang inhibition, which leads to relative hyperactivity of yang qi. JST tonifies the yin of the spleen, stomach, and lungs of those with consumptive disease, and it improves concentration and focus. JST has 13 components that exhibit several effects, including nourishing the yin, clearing deficiency heat, replenishing qi, eliminating pain, and improving the digestive function (6). Therefore, we hypothesized that JST may be an effective Kampo formula for ameliorating the symptoms of pulmonary MAC disease.

The purpose of this study was to determine the efficacy of JST in treating pulmonary MAC disease with respect to improving the physical, psychiatric, and immunological findings of affected patients.

2. Methods

2.1 Study design

This was a single-center, open-label study, conducted at the University of Fukui Hospital. Patients with a confirmed diagnosis of pulmonary MAC and those who had not yet received standard antimicrobial therapy were treated with 3.0 g of JST extract (Tsumura Co., Tokyo, Japan) three times per day. Their weight, chronic obstructive pulmonary disease assessment test (CAT) score (7–10), NK cell activity, chest computed tomography (CT) results, blood sample results, Self-rating Depression Scale (SDS) scores (11), and State-Trait Anxiety Inventory (STAI) scores (12,13) were measured at the following three points in time: (i) before JST administration, (ii) after 3 months, and (iii) at the end of the study. The treatment was administered for 12 months. Patients were determined to require standard treatment for MAC disease progression, if they had the following conditions: (i) new bronchiectasis, bronchiolitis, or nodules appearing in another lung lobe; (ii) the appearance of new infiltrative or cavitary shadows in the same or another lung lobe; or (iii) the appearance of fresh, blood-stained sputum. These patients were terminated from the study at that time. We evaluated the results of their laboratory tests at the end of the study. The chest CT findings were evaluated by two respiratory physicians using a simplified evaluation scale based on previously reported scales (Table 2) (14,15). At the completion of the study period, the group of patients whose CT scores increased by ≥1 point during the study was defined as the exacerbation group, and the group of patients whose CT scores remained unchanged or decreased during the study was defined as the non-exacerbation group. The primary endpoints were the symptom score (using the CAT), body weight, and NK cell activity before and 3 months after the administration of JST. The secondary endpoints were the SDS score, STAI scores for depression and anxiety, CT score for changes observed on images, exacerbation factors in the exacerbation and non-exacerbation groups, and the safety of JST treatment before and after 3 months of treatment. These parameters were evaluated the same way at the end of the study. Various cytokines and chemokines were also examined.

The study was conducted in accordance with the Declaration of Helsinki, and the protocol and informed consent documents were approved by the Ethics Committee of the Faculty of Medical Sciences of the University of Fukui (Registration No : Fukui 20170186, approval date : 21/02/2018) and they were registered in the UMIN-Clinical Trials Registry (Registration No : UMIN000033590, registration date : 01/08/2018). Written informed consent was obtained from all the patients who participated in this study.

2.2 Study population

The inclusion criteria were as follows: patients that were diagnosed with pulmonary MAC as per the diagnostic criteria (shown in Table 1) (16); those aged between 20 and 80 years; and those that were not using rifampicin, ethambutol, azithromycin, clarithromycin, streptomycin, kanamycin, rifabutin, sitafloxacin, or levofloxacin. However, the use of those drugs for less than 1 week for purposes other than the treatment of pulmonary MAC disease was allowed.

2.3 Assessment of the respiratory symptoms

Patients completed the CAT questionnaire before treatment, 3 months after, and at the end of the study. The CAT is a short, validated questionnaire to be completed by patients; it is used to assess the impact of chronic obstructive pulmonary disease on the health status. It consists of eight items (cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitations at home, confidence, sleep, and energy) that are formatted using a 6-point differential scale (7-10). As the items correspond to all chronic respiratory diseases, and the CAT can be used not only for chronic obstructive pulmonary disease but also for a wide range of respiratory diseases, it was used in our study to evaluate the results. The St. George's Respiratory Questionnaire, which was also developed for chronic obstructive pulmonary disease, is the most commonly used instrument for assessing symptoms of chronic respiratory diseases. However, the St. George's Respiratory Questionnaire uses redundant and complex algorithms and is not suitable for routine use. Previous studies (17) have shown that the CAT and St. George's Respiratory Questionnaire are strongly correlated; therefore, the CAT was chosen for this study.

2.4 Psychological tests

The SDS score and STAI score were measured before treatment, 3 months after, and at the end of the study.

The SDS score represents a patient's self-rated depression based on the answers to a questionnaire consisting of 20 items that are extracted based on a factor analytic study of depression and depressive symptoms reported by Grinker et al (18,19). Zung categorized the SDS scores according to the degree of depression as follows: 20 to 39, normal; 40 to 47, mild depression; 48 to 55, moderate depression; and ≥56, severe depression (11).

The STAI consists of two scales: the State Anxiety Scale, which indicates the susceptibility to anxiety at the time of measurement, and the Trait Anxiety Scale, which indicates susceptibility to anxiety as a personality trait. Both scales have the same format and include 20 items rated using a 4-point scale. The two types of anxiety can be differentiated by providing appropriate instructions to those completing the questionnaires. The mean (± standard deviation [SD]) values for normal adults are 36.6 points (SD, ±8.98 points) for state anxiety and 38.8 points (SD, ±9.68 points) for trait anxiety, corresponding to the 75th percentile or higher; the standard values for high anxiety are ≥42 points for state anxiety and ≥44 points for trait anxiety for males and ≥42 points for state anxiety and ≥45 points for trait anxiety for females (12).

2.5 Assessments of inflammation, nutritional status, NK cell activity, cytokines, and chemokines

The erythrocyte sedimentation rate, white blood cell (WBC) count, and C-reactive protein (CRP) level were measured to assess inflammation. Lymphocyte count and albumin, total cholesterol, and cholinesterase levels were measured to assess the nutritional status. Additionally, the Controlling Nutritional Status (CONUT) values were calculated using the CONUT method, which considers the lymphocytes, albumin, and total cholesterol (Table 3) (20). NK cells are mainly found in the bloodstream and have antitumor activity in a nonsensitized state in addition to regulatory effects on the antibody production system. Morphologically, they are identified as granular lymphocytes. NK cells are present in the peripheral blood as well as in the spleen, tonsil, liver, ascites, pleural fluid, and joint synovial fluid during inflammation. By measuring the cytotoxic activity of NK cells, the biological defense mechanism can be evaluated (21).

Serum cytokine CC chemokine ligand (CCL)17/thymus and activation-regulated chemokine (TARC), interferon-α, interferon-γ, interleukin (IL)-2, IL-4, IL-5, IL-6, IL-12/IL-23 p40, IL-13, IL-17/IL-17A, IL-18/IL-1F4, and tumor necrosis factor (TNF)-α were assayed (MILLIPLEX® MAP Human Cytokine/Chemokine/Growth Factor Panel A 48 Plex Premixed Magnetic Bead Panel-Immunology Multiplex Assay; MERCK Millipore Corporation, Billerica, MA, USA). Levels of the granulocyte-macrophage colony-stimulating factor was measured using an enzyme-linked immunosorbent assay (Quantikine; R&D Systems, Minneapolis, MN, USA).

2.6 Assessment of the CT images

Our scoring system (Table 2) was created by modifying previously used scoring systems (15,16). Two independent **pulmonologists** retrospectively evaluated the chest CT images and completed the scoring sheets. In case of discrepancies in their readings, the final decision was made upon reaching a consensus.

Scores were determined by considering the presence, severity, and extent of the following five categories of parenchymal abnormality: bronchiectasis (maximum score of 6); cellular bronchiolitis (maximum score of 6); cavitation (maximum score of 6); nodules (maximum score of 3), and consolidation (maximum score of 3). Therefore, a maximum total CT score of 24 was used to quantify the parenchymal lesions throughout both the lungs in each patient.

Bronchiectasis was considered to be present when the diameter of the bronchial lumen was greater than that of the adjacent pulmonary artery without tapering. Bronchiolitis (the cellular or inflammatory type) was defined as the presence of centrilobular small nodules (diameter, <10 mm) and a tree-in-bud pattern on high-resolution CT images. Other parenchymal abnormalities, such as cavitation nodules (diameter, 10–30 mm) and airspace consolidation, were also documented (Figure 1).

2.7 Safety evaluation

To determine the safety of administering JST, we observed the patients for the occurrence of any side effects. Pseudohyperaldosteronism is a serious side effect of JST that is indicated by increased blood pressure and sodium levels, fluid

retention, edema, hypokalemia, and associated myopathy (weakness, limb cramps, and paralysis). Other side effects, such as anorexia, gastric discomfort, nausea, diarrhea, and other gastrointestinal symptoms, can also be seen with JST.

To ensure patient safety while evaluating pulmonary MAC disease, only patients (i) that were not on the standard treatment of rifampicin, ethambutol, and clarithromycin combination therapy; (ii) those with stable disease; and (iii) those who could participate in follow-up were included. Therefore, if patients experienced disease progression, then they were terminated from the study and consequently, the standard treatment was administered to them.

2.8 Assessment and statistical analysis

We compared the CAT score, body weight, NK cell activity, SDS score, STAI score, CT score, various cytokines, and chemokines before treatment, 3 months after, and at the end of the study for the entire treatment group, the exacerbation group, and the non-exacerbation group using Wilcoxon's signed rank test.

Additionally, to determine if there were any differences between the non-exacerbation and exacerbation groups before treatment, the pretreatment CAT score, body weight, NK cell activity, SDS score, STAI score, CT score, various cytokines, and chemokines were compared using the Mann–Whitney U test. If significant, then the cutoff value for exacerbation was estimated using the receiver-operating characteristic curve.

3. Results

Twenty-four patients were enrolled between March 1, 2018, and January 31, 2020. Of the 24 patients initially enrolled in the study, one patient dropped out after 2 weeks of treatment because of worsening liver dysfunction, and two patients dropped out because they did not wish to continue their participation in the study. Because of worsening symptoms, one patient was terminated from the study after 3 months, two patients were after 6 months, and one patient after 10 months. Treatment for these patients was changed to standard therapy. Of the 21 patients (excluding the 3 patients who dropped out), 4 patients who did not complete the study period of 12 months and 6 patients that exhibited worsened CT scores at the end of the 12 months were included in the exacerbation group, resulting in a total of 10 patients; 11 patients whose CT scores did not worsen at the end of 12 months were included in the non-exacerbation group (Figure 2).

3.1 Characteristics of patients with MAC before JST administration

Table 4 shows the patients' characteristics. The median BMI was 19.0±2.6 kg/m^2, indicating that the patients were lean, and the median SDS score was 43±7.9 points, which is consistent with Zung's classification of mild depression (12). Their erythrocyte sedimentation rate was increased, but both the WBC counts and CRP levels were within normal limits. Regarding nutritional indices, lymphocytes, albumin, total cholesterol, and cholinesterase were within normal limits, and the CONUT levels were also normal.

3.2 Changes observed in patients with pulmonary MAC disease treated with JST

Table 5 shows the changes in all patients with pulmonary MAC disease before and 3 months after the administration of JST. There were no significant differences in the primary endpoints (the CAT score, body weight, or NK cell activity) after 3 months of treatment. The SDS score, which was a secondary endpoint, improved significantly ($p < 0.05$) after 3 months of treatment, but characteristic anxiety and state anxiety did not differ significantly. At the end of treatment, the SDS score improved significantly ($p < 0.05$) and so did the state anxiety ($p = 0.073$). According to the laboratory data, there were no significant changes after 3 months; however, at the end of treatment, lymphocytes ($p < 0.05$), albumin ($p < 0.01$), and cholinesterase ($p < 0.05$) decreased significantly, whereas the CONUT score increased significantly ($p < 0.05$) (Figure 3). There was no change in NK cell activity. Among the cytokine chemokines, CCL17/TARC decreased significantly ($p < 0.05$) and TNF-α showed an upward trend ($p = 0.076$).

3.3 Changes before and after JST treatment in the exacerbation and non-exacerbation groups

There was no difference in body weight or BMI between the two groups. The CAT score showed few changes after 3 months; however, at the end of treatment, it worsened in the exacerbation group and improved in the non-exacerbation group. The SDS score did not improve in the exacerbation group; however, it improved significantly in the non-exacerbation group at the end of treatment ($p < 0.05$). There was no significant change in blood test results after 3 months of treatment. However, at the end of treatment, the nutritional evaluation results showed that the level of lymphocytes and albumin significantly reduced in the exacerbation group before and after treatment with JST, CONUT score worsened in both groups, and cholinesterase significantly decreased in the non-exacerbation group; this change was well within normal level. There was no improvement in the NK cell activity in the exacerbation group; however, it improved in the non-exacerbation group, although the difference was not statistically significant ($p = 0.075$). In the non-exacerbation group, CCL17/TARC decreased significantly before and after JST treatment ($p < 0.05$). IL-18 also increased in the exacerbation group ($p = 0.074$), and TNF-α increased significantly ($p = 0.05$). The levels of interferon-γ, IL-4, IL-5, IL-6, IL-12/IL-23 p40, IL-13, IL-17/IL-17A, and granulocyte-macrophage colony-stimulating factor were below the sensitivity level (Table 6, Figure 4).

3.4 Comparison of the exacerbation group and non-exacerbation group data before JST administration

Table 7 shows the values of all the parameters before JST was administered to the exacerbation and non-exacerbation groups. The median ages of the patients were 66.5±9.5 years in the exacerbation group and 72±10.2 years in the non-exacerbation group. The median BMI was significantly lower in the exacerbation group (17.65±1.9 kg/m^2) than in the non-exacerbation group (20.4±2.8 kg/m^2) ($p<0.05$). In the exacerbation group, the median SDS score was 42.5±7.3 points; in the non-exacerbation group, the median SDS score was 46±8.2 points. These values were consistent with Zung's classification of mild depression. The median CT score was significantly higher in the exacerbation group (9±3.7 points) than in the non-exacerbation group (5±3.1 points) ($p < 0.01$). There was no difference between the exacerbation and non-exacerbation groups with regards to inflammatory markers, such as erythrocyte sedimentation rate, WBC, and CRP. Furthermore, there was no significant difference in lymphocytes, albumin, total cholesterol, and cholinesterase levels, along with the CONUT values, between the two groups.

The median NK cell activity levels were 43±14.8% overall, 39.5±13.9% in the exacerbation group, and 45±15.8% in the non-exacerbation group, with no significant differences between the two groups. Although normal, all these values were within the upper limits of the normal to high range, compared to the adult standard value of 18% to 40%. There was no significant difference in the cytokine chemokine levels of the two groups (Table 7). The BMI and CT score, which differed significantly between groups before JST treatment, were examined using the receiver-operating characteristic curve (Figure 5). The BMI showed a sensitivity of 72.7%, specificity of 80.0%, and an area under the blood concentration time curve of 0.768 with a cutoff value of 19.2 ($p < 0.05$); however, the CT score had a sensitivity of 80.0%, specificity of 63.6%, and an area under the blood concentration time curve of 0.732 with a cutoff value of 6.5 points ($p = 0.073$).

3.5 Comparison of the exacerbation group and non-exacerbation group data after JST administration

A comparison of the exacerbation and non-exacerbation groups after JST treatment showed that the CAT score, CT score, WBC level, and CRP level were lower in the non-exacerbation group than in the exacerbation group (all $p < 0.05$). Additionally, the STAI score for state anxiety was significantly lower in the non-exacerbation group than in the exacerbation group ($p < 0.05$).

A comparison of NK cell activity and cytokine chemokines in the exacerbation and non-exacerbation groups showed that the IL-18 level was higher in the exacerbation group than in the non-exacerbation group at the end of JST treatment ($p = 0.051$) (Supplementary Materials 1 and 2).

3.6 Safety evaluation

None of the patients treated with JST experienced any of the serious side effects listed on the package insert, including pseudohypoaldosteronism and myopathy, or any of the minor side effects, such as anorexia, gastric discomfort, nausea, and diarrhea. One patient with mild hepatic dysfunction (equivalent to the Common Terminology Criteria for Adverse Events grade 1) (22) before treatment was removed from the study because of further increase in aspartate aminotransferase and alanine aminotransferase levels (within the range of the Common Terminology Criteria for Adverse Events grade 1) after treatment with JST; however, the relationship between these effects and JST is not clear.

Regarding the safety assessment of pulmonary MAC disease, standard drug therapy was initiated for the four patients who were removed from the study because of disease progression. These patients received appropriate therapeutic intervention based on their symptoms and imaging evaluations.

4. Discussion

Pulmonary MAC disease is common in middle-aged and elderly women who are lean (23). Similar patient characteristics were observed in this study, suggesting that low BMI is an aggravating factor for pulmonary MAC. Previous reports have shown that BMI was significantly lower in the exacerbation group of pulmonary MAC disease than in the stable group (24), and that low BMI is a risk factor for mortality (25). Lean muscles with reduced respiratory and reduced expiratory forces can lead to air trapping, chronic inflammation may result in hyponutrition and weight loss, whereas bacterial colonization may persist and worsen because of decreased drainage of the peripheral airways (26).

The present study also suggested that patients with pulmonary MAC disease have high levels of anxiety and mild depression. Additionally, symptoms of depression have been observed in a high proportion of patients with pulmonary NTM disease (2).

JST is a combination of Shoyusang's components (Japanese angelica root, peony root, atractylodes rhizome, poria sclerotium, Mentha herb, bupleurum root, and glycyrrhiza), which are effective for treating irritability and malaise, and citrus unshiu peel and cyperus rhizome, which are effective for treating depression. Additionally, it contains herbal medicines with moisturizing, heat-clearing, and expectorant-tussive effects, such as ophiopogon tuber, fritillaria bulb, lycium bark, and anemarrhena rhizome. JST is used in the treatment of prolonged respiratory illnesses that cause cough, phlegm, and slight fever. It also calms the autonomic nervous system and cures the irritability and nervousness caused by mental stress (27). Glycyrrhiza, lycium bark, and citrus unshiu peel have antidepressant and anxiolytic effects. Atractylodes rhizome, poria sclerotium, bupleurum root, glycyrrhiza, ophiopogon tuber, fritillaria bulb, citrus unshiu peel, and cyperus rhizome have anti-inflammatory effects (28–34). Additionally, bupleurum root, glycyrrhiza (35), and anemarrhena rhizome (36) have anti-allergic effects, whereas glycyrrhiza and Mentha herb have antibacterial and antifungal effects, respectively (37,38). Peony root has anti-inflammatory, anti-allergic, fibrosis-inhibiting, and apoptosis-inhibiting effects (39,40). Atractylodes rhizome and glycyrrhiza have immunomodulating effects (41,42).

We hypothesized that JST administration would improve respiratory symptoms, weight loss, immune function, and psychiatric symptoms in patients with pulmonary MAC disease. The primary endpoints were the CAT score, body weight, and NK cell activity after 3 months. The results showed that there were no significant changes in these endpoints after 3 months. However, the SDS score showed a significant improvement, proving that JST improves depression.

The exacerbation group showed only slight improvement in the SDS score with JST, whereas the non-exacerbation group showed significant improvement. According to the evaluation of STAI, both state anxiety and trait anxiety were increased, up to above the normal adult levels before drug administration; however, there was no difference between the exacerbation and non-exacerbation groups. There is a strong correlation between the parameters of STAI and SDS (43), but this study showed a discrepancy between them. The STAI is an anxiety test that was standardized in Japan by Mizuguchi et al. and developed by Spielberker et al. based on the trait and state model of anxiety theory (13). The STAI consists of two scales: state anxiety, which represents the degree of anxiety at the time of the current transient measurement, and trait anxiety, which represents the tendency toward anxiety as a personality trait. The SDS, however, is a psychological test consisting of 20 questions that was developed by Zung in 1965 (12). It assumes the absence of physical illness and incorporates physical symptoms, such as weight loss and anorexia, as indicators of depression. In the present study, the non-exacerbation group did not gain any weight after JST treatment, and it is unlikely that the improvement in clinical symptoms alone had an effect. Additionally, lymphocytes and albumin significantly decreased in the exacerbation group over the course of the study. These decreases may have been suppressed in the non-exacerbation group. However, the fact that the SDS

score improved rather than remained unchanged suggests that there may be additional factors involved that determine the presence of depression apart from weight parameters alone. Therefore, JST was considered to be effective.

In the non-exacerbation group, NK cell activity showed an increasing trend before and after JST administration. Though a complementary rise in NK cell activity occurs with the administration of Chinese medicine (4). In contrast, in this study, NK cell activity did not increase in all the patients that were administered JST; it only increased in the non-exacerbation group. NK cell activity reportedly decreases in patients with mood disorders (major depression and bipolar disorder) (44). In the present study, in the non-exacerbation group, NK cell activity improved and the SDS score improved significantly. IL-18 enhances Th1 cell activation and NK cell activity (45), and we investigated the relationship between IL-18 and Th1 cell activation in the exacerbation group. IL-18 increased in the exacerbation group before and after JST treatment, and it was higher in the non-exacerbation group after treatment. Although this may be related to the Th1 cell predominance of pulmonary MAC disease, it was not related to NK cell activity. Furthermore, in this study, NK cell activity increased in the non-exacerbation group after JST treatment, suggesting that the cause of the increase may not be explained entirely by the increase in IL-18. Further studies are required to elucidate the mechanism of pulmonary MAC disease.

In this study, the antidepressant effect of JST and the improvement in respiratory symptoms were observed in the non-exacerbation group. Therefore, in our humble opinion, we believe that it is important to identify the non-exacerbation group at the time of the initial diagnosis and to administer JST. The non-exacerbation group had higher BMI and lower CT scores than the exacerbation group before JST administration. A receiver-operating characteristic curve was created, the cutoff value for BMI was 19.2, sensitivity was 72.7%, and specificity was 80.0%. Although there was no significant difference in the CT values, the cutoff value for the CT score was 6.5, sensitivity was 80.0%, and specificity was 63.6%.

Additionally, nutritional indices, such as lymphocytes, albumin, cholinesterase, and the CONUT score, worsened before and after JST treatment. Because all groups received JST, it could not be determined whether the worsening was caused by JST treatment or the disease itself. The overall trend of worsening TNF-α and the significant worsening of TNF-α in the exacerbation group suggest that inflammation worsened as the disease progressed. However, despite the exacerbation of inflammation and nutrition, the CAT score improved in the non-exacerbation group, directly suggesting an improvement in the respiratory symptoms, which is another effect of JST confirmed by this study.

CCL17, also known as TARC, is a member of the CC chemokine family that is highly expressed in the thymus and other cells, including keratinocytes, endothelial cells, dendritic cells, bronchial epithelial cells, and fibroblasts (46). CCL17/TARC has an important role in T-cell development, mature T-cell trafficking, and activation in the thymus (47). Reduced serum CCL17/TARC levels have been suggested to be a predictor of severe disease in patients with the novel coronavirus disease (48). In the present study, CCL17/TARC was decreased in the non-exacerbation group treated with JST. CCL17/TARC is mainly produced and induced by the Th2 cytokines. The fact that CCL17/TARC decreased with time suggests that the influence of Th2 is reduced in the non-exacerbation group. In the present study, CCL17/TARC was not significantly different in the exacerbation group, but it was significantly decreased in the non-exacerbation group, suggesting that the influence of Th2 is more strongly reduced in the non-exacerbation group. However, IL-18, which activates the Th1 cells, increased in the exacerbation group after JST treatment and was higher than that in the non-exacerbation group, suggesting that the Th1/Th2 balance may be slightly different in the exacerbation and non-exacerbation groups with pulmonary MAC disease. Because the aforementioned effects could not be determined by this study alone, further investigation is needed. Furthermore, whether JST treatment affected the CCL17/TARC results could not be determined through the results of this study alone.

Despite the evaluation of a large number of findings, this study had some limitations. There were only 24 patients in this study, and the sample sizes of the non-exacerbation and exacerbation groups were small; therefore, statistical analyses were unable to reveal medically significant differences. Additionally, a multivariate analysis of the non-exacerbation group could not be performed because of the small number of patients. This was a single-center study, and the number of patients that could be enrolled during the study period was limited. In addition, it was not possible to estimate whether patients would be placed in the exacerbation or non-exacerbation group; therefore, it was difficult to set a target number of patients for each group in advance. Furthermore, as this study was not a double-blind, comparative study, it did not include a control group given a placebo drug. Furthermore, it did not include blinding of the participants for placement in treatment or placebo groups either. Unfortunately, it was not feasible to obtain a suitable placebo medication at this time, because the effects of JST on MAC are hitherto unknown. Therefore, it is unclear whether the worsening of the nutritional status and inflammation are natural consequences of the progression of pulmonary MAC disease or the effects of JST. Double-blind, comparative studies should be conducted in the future to further investigate the effects of JST. We therefore consider this as a preliminary study, to be followed by double-blind, comparative studies that will be conducted later.

The most recent guidelines suggest that the mild disease group should be treated aggressively. We initially considered an evaluation of two groups—standard treatment group and standard treatment plus Chinese herbal medicine group—for our study design. However, we feared that it would not be possible to examine whether the changes in the findings were attributable to the effects of JST; therefore, we chose a different study design. In actual clinical practice, many patients with very mild cases of MAC are merely observed and do not receive any treatment; however, this study demonstrated the effects of JST on MAC patients at that stage. In addition, while many patients with pulmonary MAC are under observation without exacerbation, there are patients with exacerbation who require treatment. In this context, it is clinically meaningful to estimate exacerbation factors by comparing the exacerbation group with the non-exacerbation group, and to pre-emptively identify those who are likely to have an exacerbation.

5. Conclusion

In our study, JST resulted in an overall improvement in depression. This improvement was stronger in the non-exacerbation group than in the exacerbation group, suggesting an underlying role of NK cell activity. JST treatment for patients with high BMI and low CT scores may significantly improve respiratory symptoms (such as cough) and depression and prevent disease progression, even if the nutritional status worsens. Therefore, JST seems to be an effective treatment for selected patients with pulmonary MAC disease.

Abbreviations

MAC, *Mycobacterium avium-intracellulare* complex; JST, Jiinshihoto; SDS, Self-rating Depression Scale; BMI, body mass index; NTM, nontuberculous mycobacteria; NK cell, natural killer cell; CAT, chronic obstructive pulmonary disease assessment test score; STAI, State-Trait Anxiety Inventory; CT, computed tomography; WBC, white blood cell; CRP, C-reactive protein; CONUT, Controlling Nutritional Status; CCL, CC chemokine ligand 17; TARC, thymus and activation-regulated chemokine; TNF, tumor necrosis factor

Declarations

Ethics approval and consent to participate

The protocol and informed consent documents were approved by the Ethics Committee of the Faculty of Medical Sciences of the University of Fukui. Written informed consent was obtained from all the patients who participated in this study (Fukui 20170186), which has been registered in the UMIN-Clinical Trials Registry (000033590).

Consent for publication

Not applicable

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

MY planned and performed the research and drafted the manuscript. YW and KO proposed and planned the research. SK, KY, KK, RC, TT, MS, KN, MM, AS, TS, CH, MK, YU, and MA helped coordinate the research and assisted with various procedures. TI coordinated the research group. All authors have read and approved the final manuscript.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Table 1

Clinical and microbiologic criteria for the diagnosis of nontuberculosis mycobacterial pulmonary disease*

Clinical	Pulmonary or Systemic symptoms	Both clinical and radiological criteria required
Radiological	Nodular or cavitary opacities on chest radiograph or a high-resolution computed tomography image that shows bronchiectasis with multiple small nodules	
And	Appropriate exclusion of other diagnoses	
Microbiological†	1) Positive culture results from at least two separate expectorated sputum samples. If the results are nondiagnostic, then consider repeating the sputum AFB smears and cultures	
	Or	
	2) Positive culture results from at least one bronchial wash or lavage	
	Or	
	3) Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture-positive for NTM	

Source: Official ATS/IDSA statement [5].

*Expert consultation should be obtained when NTM are discovered that are either infrequently encountered or that usually represent environmental contamination. Patients who are suspected of having NTM pulmonary disease but do not meet the diagnostic criteria should be followed-up until the diagnosis is firmly established or excluded. Making the diagnosis of NTM pulmonary disease does not always necessitate therapy. This decision is based on the potential risks and benefits of therapy for individual patients.

†When two positive cultures are obtained, the isolates should be the same NTM species (or subspecies in the case of *M. abscessus*) to meet the disease criteria.

AFB, acid-fast Bacilli; NTM, nontuberculous mycobacteria.

Table 2

CT scoring system used to assess the extent of *Mycobacterium avium-intracellulare* complex disease

	Score			
CT findings	**0**	**1**	**2**	**3**
Bronchiectasis				
Severity	Absent	Mild (bronchus diameter > adjacent vessel diameter)	Moderate (bronchus diameter = 2-3 × vessel diameter)	Severe (bronchus diameter >3 × vessel diameter)
Extent	Absent	1-5 segments	6-9 segments	>9 segments
Bronchiolitis				
Severity	Absent	Mild (identifiable; peripheral lung <2 cm from the pleura)	Moderate (definite; involvement >2 cm from the pleura)	Severe (extensive; extending to the central lung)
Extent	Absent	1-5 segments	6-9 segments	>9 segments
Cavity				
Severity	Absent	Mild (diameter <3 cm)	Moderate (diameter, 3 cm to 5 cm)	Severe (diameter, ≥5 cm)
Extent	Absent	N = 1-3	N = 4-5	N >5
Nodules (diameter, 10-30 mm)				
Extent	Absent	1-5 segments	6-9 segments	>9 segments
Consolidation	Absent	<3 segments	3-5 segments	>5 segments

CT, computed tomography.

Table 3

Assessment of the degree of undernutrition according to the Controlling Nutritional Status

	Undernutrition degree			
Parameter	**Normal**	**Light**	**Moderate**	**Severe**
Serum albumin (g/dL)	3.5-4.5	3.0-3.49	2.5-2.9	<2.5
Score	**0**	**2**	**4**	**6**
Total lymphocytes/mL	>1600	1200-1599	800-1199	<800
Score	**0**	**1**	**2**	**3**
Screening total score	**0-1**	**2-4**	**5-8**	**9-12**

Table 4

Clinical features of the patients diagnosed with *Mycobacterium avium-intracellulare* complex disease

Characteristic	All patients (n = 21)
Age (y)	70 (47–79), 9.6
Sex, male/female	6/15
BMI (kg/m^2)	19.0 (13.9–25.1), 2.6
Deteriorated group/not deteriorated group	10/11
CAT	10 (2–28), 6.5
STAI (trait anxiety)*	43 (30–73), 10.1
STAI (state anxiety)†	44 (32–64), 7.2
SDS‡	43 (24–57), 7.9
CT score	7 (2–15), 3.9
Erythrocyte sedimentation rate (mm/1 h)	17 (2–56), 18.0
WBC count (/μL)	4900 (3800–9400), 1437.6
Lymphocytes (%)	1675.2 (896.7–3040), 513.9
CRP (mg/L)	0.06 (0.02–2.2), 0.6
LDH (U/L)	181 (144–226), 21.0
Total Protein (g/dL)	7.1 (4.0–8.5), 0.9
Albumin (g/dL)	4.3 (3.4–4.8), 0.3
Total cholesterol (mg/dL)	205 (144–261), 32.7
Cholinesterase (U/L)	307 (226–602), 85.6
CONUT score	1 (0–6), 1.54

Each item is expressed as median (min–max), SD.

*State-Trait Anxiety Inventory (trait anxiety), mean ± SD for normal adults: 38.8±9.68.

†State-Trait Anxiety Inventory (state anxiety), mean ± SD for normal adults: 36.6±8.98.

‡Self-rating Depression Scale: 20–39, normal; 40–47, mild depression; 48–55, moderate depression; ≥56, severe depression.

BMI, body mass index; CAT, chronic obstructive pulmonary disease assessment test; CONUT, Controlling Nutritional Status score; LDH, lactate dehydrogenase; SD, standard deviation; WBC, white blood cell.

Table 5

Evaluation of changes before and after Jiinshihoto administration to patients with pulmonary *Mycobacterium avium* complex disease

	Before	After 3 months	P value	End of treatment	P value
Body weight (kg)	46.5 (35.2–67.0), 8.6	46.2 (35.3–67), 8.9	0.304	45.9 (35.9–63.5), 8.4	0.465
BMI (kg/m^2)	19 (13.9–25.1), 2.6	19.4 (13.9–25.5), 2.8	0.275	18,8 (14.5–24.6), 2.6	0.525
CAT (points)	10 (2–28), 6.5	10 (0–25), 6.8	0.647	10 (0–25), 7.8	0.952
STAI (trait anxiety)	43 (30–73), 10.1	43 (30–73), 9.5	0.349	40 (28–75), 11	0.541
STAI (state anxiety)	44 (32–64), 7.2	44 (32–64), 9	0.931	42 (26–61)7.6	0.073
SDS	43 (24–57), 7.9	38 (23–55), 8.5	0.036*	41 (26–52), 7.2	0.02*
Blood findings					
Erythrocyte sedimentation rate (mm/h)	17 (2–56), 18.0	19 (3–63), 19.0	0.586	19 (3–90), 26.6	0.364
WBC count (/μL)	4900 (3800–9400), 1437.6	5000 (3500–10600), 1713.1	0.575	5000 (3000–14300), 2442.8	0.768
Lymphocytes (%)	1675.2 (896.7–3040), 513.9	1397.4 (668–2784), 491.6	0.106	1242 (664–2519), 592.3	0.042*
CRP (mg/L)	0.06 (0.02–2.2), 0.6	0.05 (0.01–2.41), 0.5	0.468	0.07 (0.01–13), 3	0.965
LDH (U/L)	181 (144–226), 21.0	176 (143–217), 19.2	0.095	193 (150–215), 17.3	0.38
Total protein (g/dL)	7.1 (4–8.5), 0.9	7.1 (3.8–8.2), 0.8	0.086	7.1 (3.8–8.2), 0.9	0.301
Albumin (g/dL)	4.3 (3.4–4.8), 0.3	4.2 (3.1–4.7), 0.4	0.133	4.1 (2.5–4.7), 0.5	0.008*
Total cholesterol (mg/dL)	205 (144–261), 32.7	201 (122–263), 32.9	0.554	195 (100–252), 37.4	0.144
Cholinesterase (U/L)	307 (226–602), 85.6	308 (202–583), 85.9	0.154	298 (158–535), 77.3	0.03*
CONUT score	1 (0–6), 1.54	2 (4–0), 1.3	0.084	2 (0–7), 1.9	0.014*
NK cell activity (%)	43 (19–67), 14.8	47 (14–70), 16.6	0.251	54.5 (19–69), 19	0.455
Cytokines and chemokines					
CCL17/TARC (pg/mL)	595.18 (211.55–1453.13), 347.6	562.57 (220.28–2095.76), 429.2	0.159	465.01 (284.93–2095.76), 433.9	0.019*
IL-2 (pg/mL)	1.05 (0.46–4.04), 0.89	1.64 (1.05–3.43), 1.11	0.505	1.3 (1.05–3.43), 0.75	0.549
IL-18 (pg/mL)	142.47 (54.99–488.22), 105.2	151.51 (64.4–767.83), 151.6	0.768	151.51 (54.99–767.83), 187.6	0.334
TNF-α (pg/mL)	2.25 (0.19–6.18), 1.4	1.52 (0.7–6.79), 1.9	0.794	2.25 (0.7–10.41), 2.3	0.076

*P < 0.05. Each item is expressed as median (min–max), SD.

BMI, body mass index; CAT, chronic obstructive pulmonary disease assessment test; CCL, CC chemokine ligand; CONUT, Controlling Nutritional Status; CRP, C-reactive protein; IL, interleukin; NK, natural killer; SDS, Self-rating Depression Scale; STAI, State-Trait Anxiety Inventory; TARC, thymus and activation-regulated chemokine; TNF, tumor necrosis factor; WBC, white blood cell.

Table 6

Evaluation of changes before and after the administration of Jiinshihoto in exacerbation and non-exacerbation groups

	Exacerbation group (n = 10)					Non-exacerbation group (n = 11)				
	Before	After 3 months	P value	End of treatment	P value	Before	After 3 months	P value	End of treatment	P value
Body weight (kg)	43.6 (37.1–58), 5.8	43.7 (37.4–58), 5.7	0.953	44.1 (38.8–58.8), 5.8	0.76	53.9 (35.2–67), 9.2	54.1 (35.3–67), 9.6	0.169	54.9 (35.9–63.5), 8.6	0.477
BMI (kg/m^2)	17.65 (15.8–22.5), 1.9	17.65 (15.9–22.5), 1.99	1	17.4 (16.2–22.8), 2.08	0.722	20.4 (13.9–25.1), 2.8	20.1 (13.9–25.5), 3.09	0.154	19.8 (14.5–24.6), 2.86	0.594
CAT (points)	11.5 (4–18), 5.5	11.5 (4–25), 6.8	0.678	18 (6–25), 7.1	0.069	9 (2–28), 7.5	6 (0–23), 6.3	0.285	6 (0–16), 5.5	0.056
STAI (trait anxiety)	42 (30–67), 9.5	43 (30–60), 8.3	0.812	39.5 (28–75), 13.5	0.834	47 (35–73), 10.7	37 (31–64), 10.9	0.21	42 (29–57), 8.8	0.575
STAI (state anxiety)	45 (42–64), 6.3	46 (37–57), 10.7	0.444	43 (32–61), 9.5	0.154	41 (32–56), 7.4	44 (23–60), 7.6	0.526	42 (26–46), 4.2	0.221
SDS	42.5 (24–54), 7.3	39.5 (24–55), 7.9	0.206	40.5 (26–51), 7.8	0.241	46 (26–57, 8.2	37 (23–52), 9.4	0.083	42 (29–52), 6.6	0.028*
Blood findings										
Erythrocyte sedimentation rate (mm/h)	21 (2–56), 20	22 (3–67), 20.7	0.261	26.5 (7–85), 27.9	0.093	16 (7–56), 16.8	11 (4–60), 17.3	0.11	18 (3–90), 26.4	0.823
WBC (/μL)	5450 (3800–9400), 1798.9	5500 (3500–10600), 2207	0.76	5900 (3800–14300), 3012.6	0.386	4800 (3800–6800), 972.9	4400 (3500–6500), 953.7	0.261	3700 (3000–6900), 1384.5	0.23
Lymphocytes (%)	1646.9 (928–3040), 625.7	1378.9 (669–2784), 637.2	0.169	1203.2 (668–25199, 659	0.047*	1675 (896–2057), 410.6	1397 (983–192), 332.2	0.328	1428 (664–2473), 556	0.286
CRP (mg/L)	0.11 (0.02–2.2), 0.8	0.08 (0.02–2.41), 0.8	0.593	0.17 (0.04–13), 3.83	0.813	0.06 (0.02–0.18), 0.1	0.03 (0.01–0.27), 0.1	0.384	0.04 (0.01–5.25), 1.6	0.677
LDH (U/L)	183 (144–226), 23.6	176.5 (143–206), 19.9	0.041	195 (167–211), 13.4	0.284	179 (157–214), 19.5	170 (160–217), 19.2	0.657	186 (150–215), 20.2	0.878
Total protein (g/dL)	7.3 (6.4–8.5), 0.6	7.15 (6.5–7.9), 0.4	0.106	7.25 (6.5–8.1), 0.6	0.473	7.1 (4–7.9),1.0	7.1 (4–7.7), 1.1	0.526	7.0 (3.8–8.2), 1.2	0.531
Albumin (g/dL)	4.2 (3.4–4.8), 0.4	4 (3.1–4.4), 0.5	0.057	4 (2.5–4.4), 0.6	0.024*	4.3 (4–4.8), 0.2	4.2 (3.9–4.7), 0.3	0.887	4.2 (3.5–4.7), 0.3	0.168
Total cholesterol (mg/dL)	206 (167–232), 19.4	207.5 (156–236), 25.5	0.475	202 (46–231), 25.5	0.646	197 (114–261), 42.1	195 (122–263), 37.8	0.755	171 (100–252), 46.5	0.182
Cholinesterase (U/L)	278.5 (226–382), 49.7	287.5 (202–369), 58.6	0.76	284 (158–352), 57.4	0.445	327 (244–602), 102.8	308 (224–583), 100.6	0.154	310 (211–535), 88.7	0.033*
CONUT score ‖	0.5(0–6), 1.9	1 (0–4), 1.7	0.301	1.5 (0–7), 2.4	0.071	1 (0–4), 1.3	2 (0–4), 0.9	0.132	2 (0–3), 1.3	0.087

	Exacerbation group (n = 10)					Non-exacerbation group (n = 11)				
	Before	After 3 months	P value	End of treatment	P value	Before	After 3 months	P value	End of treatment	P value
NK cell activity (%)	39.5 (22–65, 13.9	41 (14–70), 18	0.798	30 (19–69), 18.1	0.286	45 (19–67), 15.8	54 (26–69), 14.3	0.142	60 (24–69), 17.8	0.075
Cytokines and chemokines										
CCL17/TARC (pg/mL)	578.98 (21.55–1338.06), 333.79	535.99 (253.64–2095.76), 561.5	0.959	396.41 (396.41–2095.76), 546.82	0.386	703.69 (277.27–1453.13), 362.07	562.57 (220.28–1195.35), 284.6	0.05	573.53 (299.94–1422.75), 327.17	0.013*
IL-2 (pg/mL)	1.05 (0.46–4.04), 1.23	2.23 (1.05–3.43), 1.24	0.905	1.05 (1.05–2.23), 0.85	0.496	1.05 (0.46–2.23), 0.68	1.05 (1.05–3.43), 1.04	0.273	1.55 (1.05–3.43), 1.06	0.107
IL-18 (pg/mL)	162.71 (73.74–488.22), 138.23	158.26 (83.03–767.83), 206.5	0.575	173.99 (89.96–767.83), 255.54	0.074	137.95 (54.99–220.8), 46.93	115.21 (64.4–185.18), 40.09	0.929	128.87 (54.99–196.34), 41.22	0.374
TNF-α (pg/mL)	2.25 (0.19–6.18), 1.9	2.25 (0.7–6.79), 2.5	0.721	2.6 (1.52–10.41), 3.08	0.05	1.89 (0.7–2.95), 0.96	1.52 (0.7–4.92), 1.31	0.865	2.25 (0.7–4.28), 1.23	0.594

*P<0.05. Each item is expressed as median (min–max), SD.

BMI, body mass index; CAT, chronic obstructive pulmonary disease assessment test; CCL, CC chemokine ligand; CONUT, Controlling Nutritional Status; CRP, C-reactive protein; IL, interleukin; NK, natural killer; SDS, Self-rating Depression Scale; STAI, State-Trait Anxiety Inventory; TARC,

thymus and activation-regulated chemokine; TNF, tumor necrosis factor; WBC, white blood cell.

Table 7

Clinical features of the exacerbation and non-exacerbation groups

Characteristic	Exacerbation group (n = 10)	Non-exacerbation group (n = 11)	P value
Age (y)	66.5 (47–79), 9.5	72 (51–79), 10.2	0.6212
Sex, male/female	1/9	5/6	0.0937
BMI (kg/m^2)	17.65 (15.8–22.5), 1.9	20.4 (13.9–25.1), 2.8	0.036*
NK cell activity (%)†	39.5 (22–65, 13.9	45 (19–67), 15.8	0.468
CAT	11.5 (4–18), 5.5	9 (2–28), 7.5	0.557
STAI (trait anxiety)‡	42 (30–67), 9.5	47 (35–73), 10.7	0.973
STAI (state anxiety)§	45 (42–64), 6.3	41 (32–56), 7.4	0.099
SDS ¶	42.5 (24–54), 7.3	46 (26–57, 8.2	0.223
CT score	9 (4–15), 3.7	5 (2–14), 3.1	0.0086*

*P < 0.05. Each item is expressed as the median (min–max), SD.

†Natural killer cells activity standard level for normal adults: 18%–40%.

‡State-Trait Anxiety Inventory (trait anxiety), mean ± SD for normal adults: 38.8±9.68,

§State-Trait Anxiety Inventory (state anxiety), mean ± SD for normal adults: 36.6±8.98

¶SDS: 20–39, normal; 40–47, mild depression; 48–55, moderate depression; ≥56, severe depression.

BMI, body mass index; CAT, chronic obstructive pulmonary disease assessment test; NK, natural killer; SDS, Self-rating Depression Scale; STAI, State-Trait Anxiety Inventory.

Figures

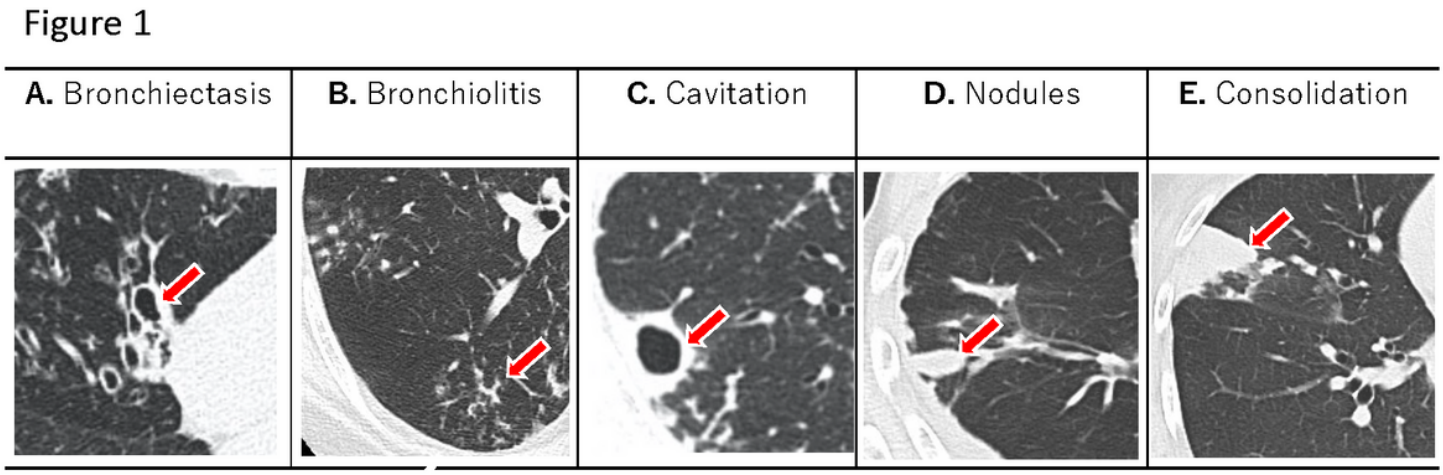

Figure 1

Inclusion criteria.

Exacerbation group (n = 10): patients with exacerbation at test completion (n = 6) and patients removed from the study because of exacerbation (n = 4). Non-exacerbation group (n =11): patients with no exacerbation at test completion.

Figure 2

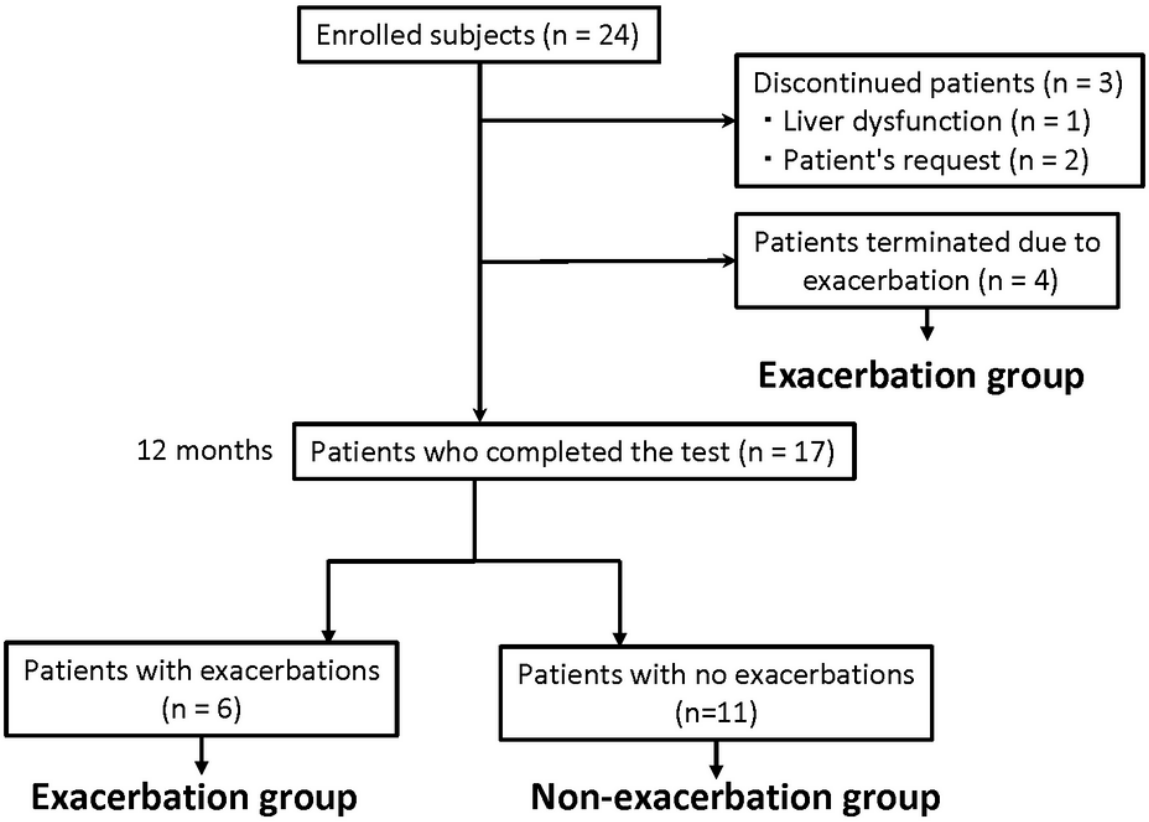

Figure 2

Five categories of the computed tomography (CT) classification of *Mycobacterium avium-intracellulare* complex (MAC) disease. A: Bronchiectasis. B: Bronchiolitis. C: Cavitation. D: Nodules. E: Consolidation.

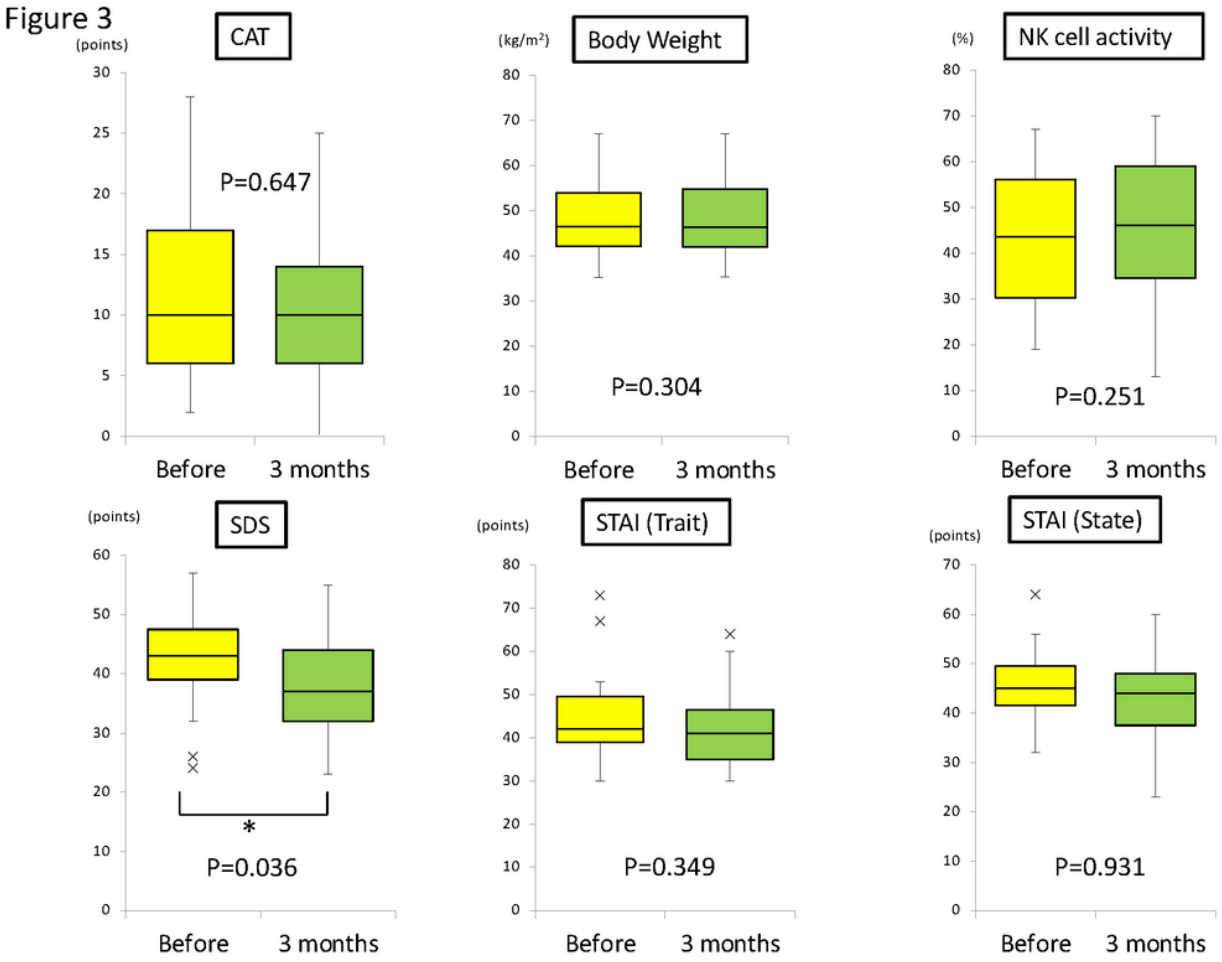

Figure 3

Changes before and 3 months after Jiinshihoto (JST) administration to all patients with pulmonary *Mycobacterium avium-intracellulare* complex (MAC) disease. There were no significant differences in the chronic obstructive pulmonary disease assessment test (CAT) score, body weight, or natural killer (NK) cell activity. Regarding the psychological tests, the Self-rating Depression Scale (SDS) score significantly improved after 3 months of treatment, but trait anxiety and state anxiety were not significantly different.

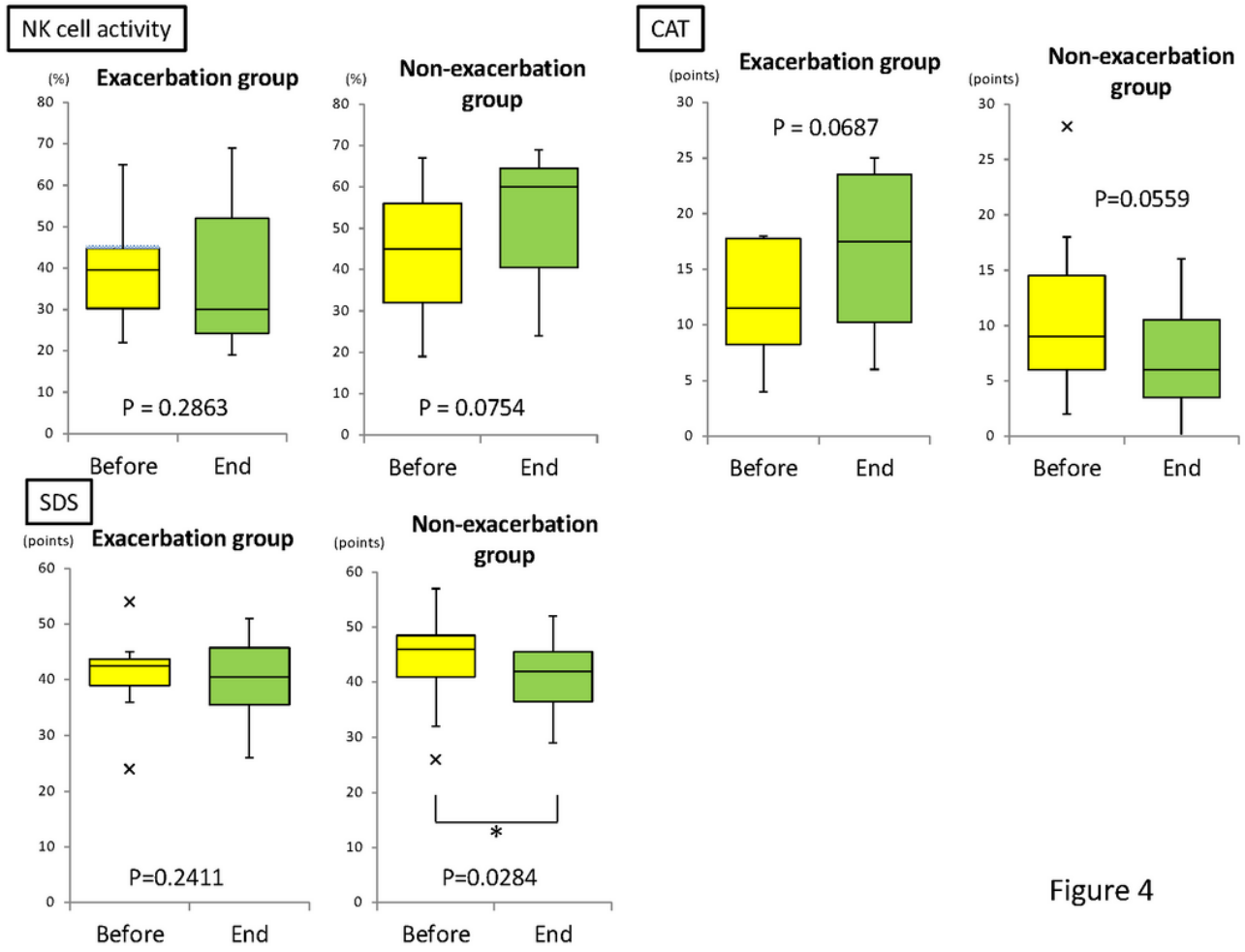

Figure 4

Changes before and after treatment with Jiinshihoto (JST) in the exacerbation and non-exacerbation groups. Natural killer (NK) cell activity improved in the non-exacerbation group. The chronic obstructive pulmonary disease assessment test (CAT) score tended to worsen in the exacerbation group but improved in the non-exacerbation group. The Self-rating Depression Scale (SDS) score did not improve in the exacerbation group, but it improved significantly in the non-exacerbation group at the end of treatment.

Figure 5

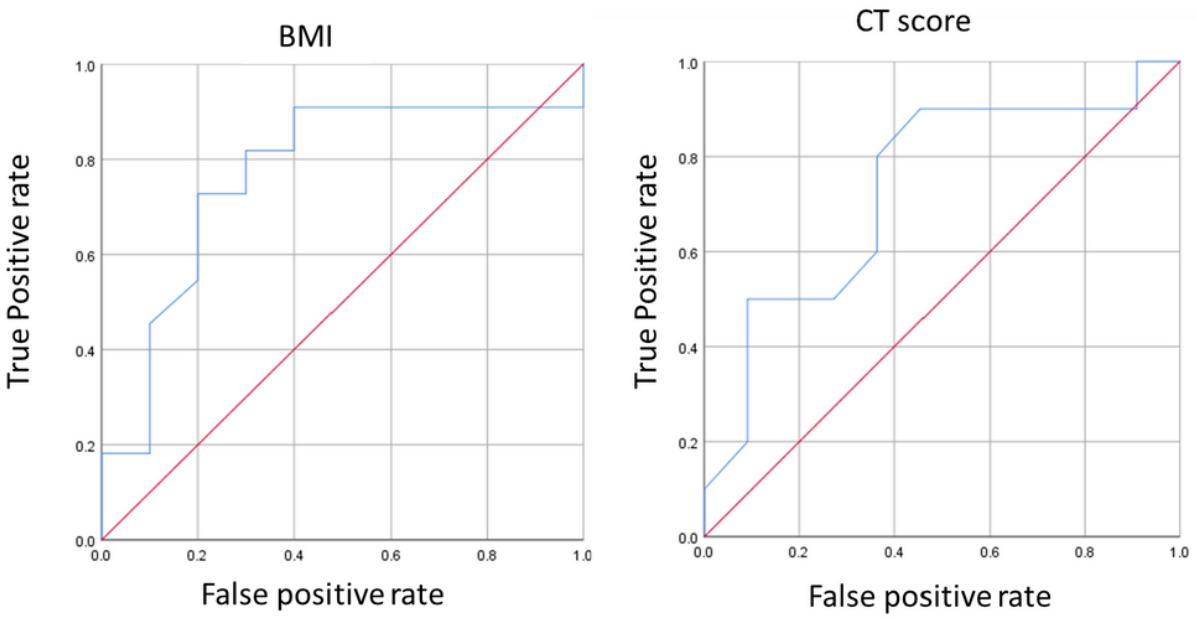

Figure 5

Receiver-operating characteristic (ROC) curve with body mass index (BMI) and computed tomography (CT) score. The BMI had sensitivity of 72.7%, specificity of 80.0%, and area under the receiver-operating characteristic curve (AUC) of 0.768, with a cutoff value of 19.2 ($p < 0.05$). The CT score had sensitivity of 80.0%, specificity of 63.6%, and AUC of 0.732, with a cutoff value of 6.5 points ($p = 0.073$).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- MACdata.xlsx
- MACJIINSHIHOTOsupplementarymaterial.pptx