The Activities of Daily Living after an Acute Exacerbation of Idiopathic Pulmonary Fibrosis

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Abstract:
Objective An acute exacerbation (AE) of idiopathic pulmonary disease (IPF) represents a life threatening condition. The activities of daily living (ADL) and quality of life of patients who survive an AE of IPF (AE-IPF) are often diminished. However, the association between AE-IPF and the ADL has yet to be evaluated.

To evaluate the effect of AE-IPF on the ADL.

Methods, Patients Patients treated for AE-IPF from 2010 to 2014 were identified. We retrospectively evaluated their ADL before and after AE-IPF using a modified Barthel index (BI) composed of 6 items.

Results Twenty-eight of the 47 AE-IPF patients remained alive at 3 months after the onset of AE-IPF. The BI values of 22 survivors (79%) showed a full score (70 points) before the onset of AE-IPF. The evaluation of the BI scores at four weeks after the onset of AE-IPF revealed that the scores of 12 patients had decreased by >15 points and more than half of the survivors showed scores of <55. Logistic regression analyses showed that persistent hypoxemia at 28 days after an AE, both at exertion (odds ratio, 24.20; 95% confidence interval, 2.42-242.31; p=0.009) and at rest (odds ratio, 21.00; 95% confidence interval, 2.05-215.18; p=0.010), was associated with a >15-point decrease in the BI score at 4 weeks after AE-IPF.

Conclusion AE-IPF survivors with persistent hypoxemia showed diminished ADL after treatment.

Key words: acute exacerbation, idiopathic pulmonary fibrosis, activities of daily living, hypoxemia, quality of life

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Introduction

Idiopathic pulmonary fibrosis (IPF) is chronic, progressive fibrotic lung disease of unknown cause (1). IPF is fatal, with death typically resulting from a slow decline in the lung function, lung cancer, or an acute exacerbation (AE) (2, 3). AE-IPF is defined by the presence of idiopathic diffuse alveolar damage causing the acceleration of fibroproliferative changes. The lack of consensus regarding prompt treatment can be life threatening and is the principal cause of death in IPF patients (4). AE-IPF survivors often have a diminished pulmonary function, activities of daily living (ADL), and quality of life (QOL).

Maintaining the QOL of IPF patients requires an accurate assessment of the extent of ADL impairment after AE-IPF. Although numerous studies have investigated the disturbance and recovery of ADL in people with stable and exacerbated chronic obstructive pulmonary disease (COPD) (5-10), few studies have examined the relationship between IPF and ADL (11, 12). Moreover, the optimal approach to assessing the ADL of IPF patients remains a matter of debate. In this retrospective study, we used the Barthel index (BI) (13), an easily calculated and widely accepted measurement, to evaluate the time course of ADL impairment after AE-IPF. The severity of ADL impairment and the factors associated with ADL impairment in AE-IPF patients were also determined.

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Materials and Methods

**Study design**

The changes in the ADL of AE-IPF patients over time (1, 8, 15, and 29 days after AE) were measured using the BI, as described below. Information on the ADL before AE-IPF was obtained from ADL evaluations that were conducted at our hospital within 3 months before the AE. If these evaluations had not been conducted at our hospital, the patients were questioned directly. The clinical findings, laboratory data, and information on the evaluation of the patients’ ADL were collected retrospectively from the patients’ medical records. Hypoxemia was defined by an SpO2 value of <90%. The presence of hypoxemia at 4 weeks after AE-IPF was assessed using a 6-minute walk test. These data were then used to assess the factors associated with a decreased BI score at 29 days after the onset of AE-IPF.

**Patients**

We reviewed the records of all patients who received a diagnosis of AE-IPF at Toho University Omori Medical Center during the period from 2010 to 2014. The definitions of IPF and AE are detailed below. There were a total of 47 AE-IPF patients. The 28 patients who were alive at 3 months after the AE were defined as survivors in the analysis.

**The diagnosis of IPF**

IPF was diagnosed retrospectively based on high-resolution computed tomography (HRCT) images and the histopathological findings from a lung biopsy, according to the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines (1). Seven patients (15%) underwent surgical lung biopsy before the onset of AE-IPF, and all specimens showed a usual pattern of interstitial pneumonia (UIP). The HRCT of all of the patients were evaluated by 2 pulmonologists (T.I. and S.S.) and 1 chest radiologist (A.K.).

**The diagnosis of AE-IPF**

The diagnostic criteria for AE-IPF were based on the definition proposed by Collard et al. (4), namely 1) a previous or current diagnosis of IPF, 2) the unexplained worsening or development of dyspnea in the past 30 days, 3) an HRCT scan showing new bilateral ground-glass opacities and/or consolidation superimposed on a background reticular or honeycomb pattern, 4) no evidence of pulmonary infection in the cultures of the patient’s bronchoalveolar lavage fluid, endotracheal aspirate, or sputum and negative results on blood tests for other potentially infectious pathogens, and 5) the exclusion of left heart failure, pulmonary embolism, and other possible causes of acute lung injury.

**The evaluation of ADL**

The ADL was assessed before and after the AE (days 1, 8, 15, and 29) using the BI (13). Although a relationship between the BI and a diminished ADL has not been demonstrated in patients with respiratory disease, we selected this index based on its convenience and wide acceptance, and because it is routinely used to evaluate the ADL of inpatients in our hospital. The BI evaluates the ADL in relation to feeding, transferring, grooming, toilet use, bathing, dressing, walking, bowel/bladder control, and ascending/descending stairs. For the purpose of this study, the categories bowel/bladder control and ascending/descending stairs were removed because they are strongly affected by the severity of respiratory failure and the type of care that is provided—including the extent of bed rest and urethral catheterization. Thus, the modified BI in our study consisted of 7 items (Table 1). The total scores ranged from 0-70, with a higher score indicating better ADL. The changes in the BI score at day 29 in comparison to before the onset of the AE were arbitrarily classified as mild (a decrease of <10 points), moderate (10-15 points), and severe (>15 points).

**Statistical analysis**

Fisher’s exact test or the χ² test and Mann-Whitney U test were used to compare the characteristics of survivors and non-survivors. The factors associated with a diminished BI score were identified by a logistic analysis. The p values of < 0.05 were considered to indicate statistical significance.

**Ethical considerations**

This study was reviewed and approved by the Institutional Review Board of Toho University Omori Medical Center (project approval No. 27-166) and was conducted according to the principles expressed in the Declaration of Helsinki.

**Results**

**Patient characteristics**

The clinical characteristics, laboratory findings, and treatments of the patients are shown in Table 2. The median age at the AE was 74 years (range, 58-86). Twelve patients received no medical treatment for the chronic progression of IPF before the AE. Diagnostic bronchoalveolar lavage and endotracheal aspiration were not performed in any of the patients because of the severity of their respiratory failure. Recombinant thrombomodulin was used to treat AE-IPF, as described previously (14). There was no significant difference in the treatments administered to the survivors and non-survivors. The survivors showed a higher PaO2/FiO2 ratio at the onset of AE-IPF in comparison to the non-survivors (p=0.008).

**Evaluation of the ADL**

The BI scores before and after AE-IPF are shown in
Table 1. Barthel Index.

| Feeding       | Bathing                  | Mobility               | Dressing                  | Grooming                  | Toilet use   |
|---------------|--------------------------|------------------------|---------------------------|---------------------------|--------------|
| 0 unable      | 0 dependent              | 0 immobile or <50 yards| 0 dependent               | 0 needs help with personal care | 0 dependent |
| 5 needs help cutting, spreading butter, etc | 5 independent (in shower) | 5 wheelchair independent. Including corners, >50 yards | 5 needs help but can do about half unaided | 5 independent face/hair/teeth/shaving (implements provided) | 5 needs some help, but can do something alone |
| 10 independent | 10 independent (on and off, dressing, wiping) |

| Transfer     | Mobility               | Dressing                  | Grooming                  | Toilet use   |
|--------------|------------------------|---------------------------|---------------------------|--------------|
| 0 unable, no sitting balance | 0 immobile or <50 yards | 0 dependent               | 0 needs help with personal care | 0 dependent |
| 5 major help (one or two people, physical), can sit | 5 wheelchair independent. Including corners, >50 yards | 5 independent face/hair/teeth/shaving (implements provided) | 5 independent face/hair/teeth/shaving (implements provided) |
| 10 minor help (verbal or physical) | 5 independent (on and off, dressing, wiping) |

| Grooming                  | Mobility               | Dressing                  | Grooming                  | Toilet use   |
|---------------------------|------------------------|---------------------------|---------------------------|--------------|
| 0 needs help with personal care | 0 immobile or <50 yards | 0 dependent               | 0 needs help with personal care | 0 dependent |
| 5 independent face/hair/teeth/shaving (implements provided) | 5 wheelchair independent. Including corners, >50 yards | 5 independent face/hair/teeth/shaving (implements provided) | 5 independent face/hair/teeth/shaving (implements provided) |
| 10 independent (on and off, dressing, wiping) | 10 independent (including buttons, zips, laces, etc) |

The original evaluation criteria for the BI comprise nine items: feeding, transferring, grooming, toilet use, bathing, dressing, walking, bowel/bladder control, and ascending/descending stairs. For this analysis, bowel/bladder control and ascending/descending stairs were excluded.

Figs. 1 and 2. The BI scores before the AE were higher among survivors than among non-survivors (p=0.023). At 4 weeks after the onset of AE-IPF, the BI scores of half of the survivors were lower than 55. The BI values of 22 survivors (79%) were highest before the onset of AE-IPF. In comparison to the survivors, a larger proportion of non-survivors had BI values of <35 on the first day of AE-IPF.

Fig. 2 shows the time course of the BI scores of the survivors. The maximum impairment was observed on days 1 or 8 for all of the ADL items. A majority of patients required some assistance in bathing or mobility at 4 weeks after AE-IPF; however, most required no assistance while eating.

Among the survivors, the severity of ADL impairment on day 29 after the AE was classified as mild, moderate, or severe. The difference in the BI change on days 1, 8, 15, and 29 after AE-IPF in the 3 groups (classified according to severity) are shown in Fig. 3. The BI value of the severe group, but not the other groups, was decreased on day 8. The BI score of the severe group on day 8 and the moderate group on day 15 showed significant differences in comparison to the mild group.

**The factors associated with severe ADL impairment after AE-IPF**

The BI scores of 12 patients changed by >15 points, indicating the severe impairment of their ADL. A previous study of stroke patients reported that a 20-point increase in the BI value reflects the need for daily assistance (15). We evaluated age, the PaO2/FiO2 ratio, the serum LDH titer, and the persistence of hypoxemia (before and 28 days after the AE) as risk factors for severe ADL impairment. The results are shown in Table 3. A logistic regression analysis showed that severe ADL impairment was associated with hypoxemia on exertion [odds ratio (OR), 24.20; 95% confidence interval (CI), 2.42-242.31; p=0.009] and at rest (OR, 21.00; 95% CI, 2.05-215.18; p=0.010) at 28 days after AE. The presence of hypoxemia before AE-IPF was not associated with severe ADL impairment (OR, 5.00; 95% CI, 0.44-55.63; p=0.190).

**Discussion**

Chronic lung diseases resulting in respiratory failure, dyspnea, and cough have a considerable adverse effect on a patient’s QOL and ADL, through the slow progression of respiratory impairment and the exacerbation of disease. Although data have accumulated on the ADL of COPD patients in recent years, few studies have evaluated the ADL of IPF patients, and most such studies have focused on chronic impairment following an AE (11, 12). This is the first report on the relationship between AE-IPF and the ADL.

We found that the ADL of IPF patients was affected by the persistence of hypoxemia after AE-IPF. The ADL scores of IPF patients are related to their Medical Research Council dyspnea grade and lung function (12), which indicates that the chronic progression of IPF impairs the ADL and sug-
Table 2. Characteristics of the AE-IPF Patients.

|                              | Survived patients (n=28) | Fetal patients (n=19) | p value |
|------------------------------|--------------------------|-----------------------|---------|
| Median age (years old)(range)| 75 (58-86)               | 74 (68-85)            | 0.914   |
| Never smoker (%)             | 4 (15%)                  | 1 (5%)                | 0.635   |
| Male (%)                     | 24 (86%)                 | 18 (95%)              | 0.635   |
| Pulmonary function before AE-IPF |                         |                       |         |
| %FVC                         | 77±19                    | 73±18                 | 0.575   |
| %FEV1.0                      | 102±22                   | 91±22                 | 0.162   |
| %DLCO                        | 52±17                    | 55±14                 | 0.571   |
| Treatment before AE-IPF     |                          |                       |         |
| CS                           | 3 (11%)                  | 5 (26%)               | 0.240   |
| Cyclosporine A               | 1 (4%)                   | 2 (11%)               | 0.557   |
| Pirfenidone                  | 5 (18%)                  | 3 (16%)               | 1.000   |
| N-acetylcysteine             | 12 (43%)                 | 6 (32%)               | 0.546   |
| No medication                | 14 (50%)                 | 8 (42%)               | 0.767   |
| Respiratory failure before AE-IPF |                       |                       |         |
| CS                           | 4 (14%)                  | 5 (26%)               | 0.453   |
| Clinical parameters at AE-IPF onset |                   |                       |         |
| White blood cell (/μL)       | 9,800±3,200              | 11,000±2,900          | 0.590   |
| C-reactive protein (mg/dL)   | 7.3±5.9                  | 8.2±4.6               | 0.174   |
| LDH (IU/L)                   | 336±70                   | 378±145               | 0.198   |
| KL-6 (U/mL)                  | 1,509±1,135              | 1,418±1,026           | 0.832   |
| SP-D (ng/mL)                 | 321±201                  | 437±348               | 0.144   |
| SP-A (ng/mL)                 | 91±39                    | 87±46                 | 0.074   |
| PaO2/FiO2 ratio              | 277±88                   | 194±111               | 0.008*  |
| Medications for AE-IPF      |                          |                       |         |
| CS pulse therapy             | 27 (100%)                | 19 (100%)             | 1.000   |
| CS maintenance therapy       | 27 (100%)                | 19 (100%)             | 1.000   |
| Cyclosporine A               | 23 (85%)                 | 15 (79%)              | 1.000   |
| Recombinant thrombomodulin   | 17 (63%)                 | 7 (37%)               | 0.143   |
| Hypoxemia after AE-IPF      |                          |                       |         |
| At rest                      | 8 (29%)                  | -                     | -       |
| On exertion                  | 9 (32%)                  | -                     | -       |
| Degree of lowering of BI after AE-IPF |                   |                       |         |
| 0                            | 6 (21%)                  | -                     | -       |
| mild (5-15)                  | 10 (36%)                 | -                     | -       |
| severe (20-)                 | 12 (43%)                 | -                     | -       |
| Median Survival duration after AE-IPF onset (days) (range) | 13 (2-82) | - | |

*p<0.01.

AE: acute exacerbation, IPF: idiopathic pulmonary fibrosis, FVC: forced vital capacity, FEV1.0: forced expiratory volume in one second, DLCO: diffusing capacity of the lung for carbon monoxide, CS: corticosteroids, LDH: lactate dehydrogenase

Figure 1. The time course of the total Barthel index (BI) score. The numbers on the bar indicate the number of patients in each BI score range.
gests that an acute decline in the pulmonary function after AE-IPF reduces the ADL in proportion to the severity of impairment. Our present findings suggest that AE-IPF patients who show hypoxemia - which reflects severe disease progression after treatment - require additional medical and social support, to maintain or improve their ADL.

The health-related consequences of an AE of COPD (AE-COPD) have been more extensively investigated than the health-related consequences of AE-IPF. Because of its adverse effects on the cognitive function and ADL, AE-COPD can reduce a patient’s QOL (5, 9, 16). Disturbances in a patient’s physical activities after AE-COPD tend to resolve within 3 weeks of the onset of the exacerbation (9). In addition to this spontaneous remission of the adverse impact on the patient’s ADL, pulmonary rehabilitation, which is a cornerstone in the management of stable disease (17), has been shown to improve patients’ activity limitations and QOL in clinical trials (18, 19) and a meta-analysis (20). However, the decrease in the ADL of AE-IPF patients is usually irreversible, as indicated by the persistent decrease in the ADL scores of the patients in the present study, particularly those with respiratory failure. In addition, Kozu et al. reported that

**Figure 2.** The time course of the total BI score of the survivors according to the severity of their condition. The numbers on the bars indicate the number of patients for each BI score.

**Figure 3.** The difference in the time courses of the BI scores of the survivors according to the BI score change on day 29. The p values for each date indicate the significance of the difference in the BI change between the 2 groups.
The authors state that they have no Conflict of Interest (COI).

Table 3. Univariate Logistic Analysis of the Risk for Lowering BI Score More than 15 Points 4 Weeks after AE-IPF.

|                      | OR(95% CI) | p value |
|----------------------|------------|---------|
| Age                  | 1.04 (0.92-1.18) | 1.040   |
| Minimum PaO2/FiO2 ratio | 1.01 (0.99-1.03) | 0.079   |
| Respiratory failure   |            |         |
| On exertion           | 24.20 (2.42-242.31) | 0.009** |
| At rest              | 21.00 (2.05-215.18) | 0.010*  |
| Before AE-IPF        | 5.00 (0.45-55.63)  | 0.190   |
| LDH                  | 0.99 (0.98-1.00)  | 0.139   |

*p<0.05, **p<0.01.

Hypoxemia was defined as an SpO2 value <90%. Hypoxemia at exertion and at rest was assessed using a 6-minute walk test on day 29 after AE-IPF. All patients with hypoxemia before AE-IPF had an SpO2 value<90% at rest.

AE: acute exacerbation, IPF: idiopathic pulmonary fibrosis, LDH: lactate dehydrogenase

pulmonary rehabilitation was less effective for IPF patients (11). This difference in the recovery after AE-IPF may be due to pathologic fibrotic changes that affect the respiratory function. Greater control of the medical and social environment may be necessary after AE-IPF in patients with respiratory failure, due to the persistent decrease in their performance of ADL.

The present study is associated with several limitations. First, it was a retrospective study of a small number of patients. Because a patient’s ADL can be affected by many factors, such as the care environment as well as their cognitive function and physical condition, a larger sample size is needed to increase the accuracy of the analysis. A second limitation is that it is unclear whether the BI is an appropriate instrument for evaluating the ADL in IPF patients. In patients with COPD, the ADL is evaluated by disease-specific indexes such as the University of California, San Diego Shortness of Breath Questionnaire (SOBQ) (21), a modified version of the Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ-M) (22, 23), and the London Chest ADL Scale (LCADL) (24). However, no such index has been created or modified to evaluate the ADL of IPF patients. A final limitation is that a longer observational period might be necessary to clarify the trends in the impairment of physical activities. A study of COPD cases revealed that the performance of ADL improved after a patient was discharged from hospital (10); however, the survivors in the present study all remained hospitalized from days 1 to 29 after the onset of AE-IPF.

AE-IPF was associated with ADL impairment. Thus, to maintain the QOL of AE-IPF survivors with persistent hypoxemia, it may be necessary to pay more attention to the factors that disturb their ADL.

The authors state that they have no Conflict of Interest (COI).

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