ORIGINAL ARTICLE

Risk factors for in-hospital mortality in patients with advanced lung cancer with interstitial pneumonia undergoing systemic chemotherapy: A retrospective and observational study using a nationwide administrative database in Japan

Tomoko Shiraishi1 | Keishi Oda1 | Kei Yamasaki1 | Takashi Kido2 | Konomi Sennari1 | Hiroshi Mukae2 | Makoto Ohtani3 | Yoshihisa Fujino4 | Shinya Matsuda5 | Kiyohide Fushimi6 | Kazuhiro Yatera1

1Department of Respiratory Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan
2Department of Respiratory Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
3Information Systems Center, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan
4Department of Environmental Epidemiology, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan
5Department of Preventive Medicine and Community Health, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan
6Department of Health Policy and Informatics, Tokyo Medical and Dental University, Tokyo, Japan

Correspondence
Kei Yamasaki, Department of Respiratory Medicine, University of Occupational and Environmental Health, Japan, 1-1 Iseigaoka, Yahatanishiku, Kitakyushu City, Fukuoka 807-8555, Japan.
Email: yamasaki@med.uoeh-u.ac.jp

Abstract
Background: The safety profile of systemic chemotherapy for lung cancer patients with interstitial pneumonia (IP) in clinical practice remains unclear. Using Diagnostic Procedure Combination (DPC) data from the Japanese administrative database, we investigated the mortality of hospitalized lung cancer patients with IP as they underwent a course of systemic chemotherapy nationwide.

Methods: The DPC data of patients with stage IIIIB or IV lung cancer as defined by the Union for International Cancer Control Tumor-Nodes-Metastases 6th and 7th editions from April 2014 to March 2016 were obtained. Among those patients, only patients with concomitant IP and receiving systemic chemotherapy without radiotherapy were included.

Results: Among 1524 included patients, 70 (4.6%) died in the hospital. Multivariate analysis revealed that low activities of daily living (ADL) scores on admission (hazard ratio [HR] 2.26, 95% confidence interval [CI] 1.24–4.12, p = 0.008) and high-dose corticosteroid therapy following chemotherapy (HR 2.62, 95% CI 1.44–4.77, p = 0.002) were strongly associated with in-hospital mortality. It was determined that patients possibly received high-dose corticosteroids for IP exacerbations; these patients had a higher in-hospital mortality rate of 67.7% (21/31 patients) and a significantly shorter median survival time of 55 days (95% CI 31–69 days, p < 0.001) than those who did not receive high-dose corticosteroids.

Conclusion: Acute exacerbation of IP treated with systemic high-dose corticosteroids is significantly associated with in-hospital mortality, and a low ADL score on admission is a risk factor for in-hospital mortality in lung cancer patients with IP who undergo systemic chemotherapy.

KEYWORDS
activities of daily living, chemotherapy, in-hospital mortality, interstitial pneumonia, lung cancer

INTRODUCTION

Lung cancer patients with interstitial pneumonia (IP) are continuously at risk for disease progression, especially acute IP exacerbations. A high mortality rate of approximately 50% within 3 months or less is usually observed in patients with acute idiopathic pulmonary fibrosis (IPF) exacerbations.1-3 It has been reported that the incidence of lung cancer is seven to 14 times higher in patients with IP than in those without IP.4 Additionally, 5–10% of patients...
with advanced lung cancer who require chemotherapy have
IP complications.5 The prognoses of lung cancer and IPF,
among the other causes of interstitial pneumonia, are simi-
lar, and whether or not aggressive systemic chemotherapy is
warranted for lung cancer patients with IP is unclear.

Systemic chemotherapy for lung cancer may extend the
prognosis of patients with concomitant lung cancer and IPFs;6,7
howver, the specific protective and risk factors in
these patients are not yet completely understood. Bessid
own risk factors for in-hospital mortality such as older
age, poor (3, 4) Eastern Cooperative Oncology Group
Performance Status (ECOG-PS), neutropenia,8 and
thromboembolism,9 treatment with systemic chemotherapy
is also a known risk factor for acute IP exacerbations in lung
cancer patients with IPF.10,11 A risk scoring system to pre-
dict acute IPF exacerbations using a patient’s smoking his-
tory, chemotherapeutic medication history, and diffusing
capacity of the lung for carbon monoxide has been pro-
posed11,12 however, the safety of chemotherapy in lung cancer
patients with IP in clinical practice remains unclear.

The Diagnosis Procedure Combination (DPC) is a Japanese
administrative claims database of inpatient care, covering
approximately 60% of all hospitalizations nationwide. The DPC
stores information on patient admission and discharge. This
includes each patient’s working diagnosis on admission, height,
weight, activities of daily living (ADL) scores, physical examina-
tion findings, and medication intake, among others.

Using the Japanese DPC database, we investigated risk
factors for mortality among lung cancer patients with IP
undergoing in-hospital systemic chemotherapy.

METHODS

Data collection

Information on each patient’s primary disease and any com-
orbidity they may have had on admission was retrieved
from the DPC database. Data on any diseases that developed
during each patient’s hospitalization were likewise collected.
Disease data were retrieved as International Classification
of Disease 10th Revision (ICD-10) codes.

Data on each patient’s age, sex, height, weight, smoking
index (based on the Brinkman index: the number of ciga-
rettes smoked per day multiplied by the number of years of
smoking), ADL score (represented by the Barthel Index),
severity of dyspnea scale score (Fletcher, Hugh-Jones dys-
pnea scale; Japanese version of the modified Medical
Research Council dyspnea scale), and medical management
details were also obtained for this study.

The DPC data of patients with stage IIIB or IV lung can-
cer as defined by the Union for International Cancer Con-
trol Tumor-Nodes-Metastases (UICC TNM) 6th and 7th ed-
itions from April 2014 to March 2016 were used. Patients
treated with radiation therapy (DPC code “M001 external
beam radiation therapy”) during hospitalization were
excluded; irradiation site data was unavailable.

Definitions

A patient was identified as having lung cancer if an ICD-10
code of C34 (malignant neoplasm of bronchus and lung)
was noted in that patient’s DPC database record (Figure 1).
Similarly, a patient was identified as having interstitial pneu-
monia if an ICD-10 code of J84, J84.1, or J84.9 (other inter-
stitial pulmonary diseases, other interstitial pulmonary
diseases with fibrosis, interstitial pulmonary disease,
unspecified) was noted in that patient’s DPC database
record. (Figure 1). Lung cancer stage was defined according
to the UICC TNM 6th and 7th editions. Since acute exacer-
bations of IP are rarely entered as a disease name in the
DPC, we investigated the use of high-dose corticosteroid
therapy to identify acute exacerbations of IP; high-dose
corticosteroid therapy is a standard treatment for acute
exacerbations of IP in Japan. We also investigated whether
the patients received high-dose corticosteroid therapy for
diseases other than IP based on the name of the primary
disease, comorbidities, and disease onset at admission.
High-dose corticosteroid therapy was defined as methyl-
 prednisolone use of 500 mg/day or more following systemic
chemotherapy for lung cancer. “Overlapping regimen” cases
were defined as patients who underwent treatment with two
or more regimens during one hospital stay.

Outcomes

The primary outcome of this study was in-hospital mortal-
ity. The secondary outcome was survival time according to
identified risk factors significantly related to in-hospital
mortality.

Statistical analysis

Statistical significance was set at \( p < 0.05 \). To determine sur-
vival, the starting point was defined as the date of admission,
the censoring point as the date of discharge, and the end
point as death. Factors involved in-hospital mortality were
analyzed using the Cox proportional hazards model. A uni-
ivariate analysis was performed on each patient factor based
on the Cox proportional hazards model, and any factors that
were statistically significant in the univariate analysis were
incorporated as covariates. A multivariate analysis was then
performed on these variables based on the Cox proportional
hazard model. In the analyses, the proportional hazard
property was examined using the Schoenfeld residual plot
for each variable. The assumption of proportional hazards
was not rejected. In addition, patient survival times were
estimated using the Kaplan–Meier method for factors that
were found to be significant in the multivariate analysis. The
log-rank test was used to assess any significant differences in
the median survival time. EZR software (Saitama Medical
Center, Jichi Medical University, Saitama, Japan) was used
for the statistical analyses as demonstrated by Kanda.13
65,535 stage IIIB or IV lung cancer cases with an ICD-10 code of C34, (Malignant neoplasm of bronchus and lung)

2,460 cases with ICD-10 diagnosis code of “interstitial lung disease*”

1,586 cases were treated with systemic chemotherapy

62 cases were excluded due to radiation therapy

1,524 cases were eligible

* Refer to Fig. 1

** FIGURE 1  ICD-10 diagnosis code of lung cancer and interstitial pneumonia cases

** FIGURE 2  Patient selection flow chart

ICD-10 diagnosis code of lung cancer cases
C34 Malignant neoplasm of bronchus and lung
   C34.0  Malignant neoplasm of main bronchus
   C34.1  Malignant neoplasm of upper lobe, bronchus or lung
   C34.2  Malignant neoplasm of middle lobe, bronchus or lung
   C34.3  Malignant neoplasm of lower lobe, bronchus or lung
   C34.8  Malignant neoplasm of overlapping sites of bronchus and lung
   C34.9  Malignant neoplasm of unspecified part of bronchus or lung

ICD-10 diagnosis code of interstitial pneumonia cases
J84 Other interstitial pulmonary diseases
J84.1 Other interstitial pulmonary diseases with fibrosis
   Diffuse interstitial pneumonia
   Diffuse alveolar damage
   Lymphocytic interstitial pneumonia
   Post-inflammatory lung fibrosis
   Combined pulmonary fibrosis and emphysema
   Acute interstitial pneumonitis
   Respiratory bronchiolitis-associated interstitial lung disease
   Usual interstitial pneumonia
   Idiopathic interstitial pneumonia
   Cryptogenic organizing pneumonia
   Idiopathic pulmonary fibrosis
   Pulmonary fibrosis
   Desquamative interstitial pneumonia
   Idiopathic non-specific interstitial pneumonitis
J84.9 Interstitial pulmonary disease, unspecified
RESULTS

Patient background

Among the 65,535 stage IIIB/IV lung cancer patients treated with chemotherapy, 1,586 had concurrent IP and were receiving systemic chemotherapy, leaving 1,524 patients that were eligible for this study (Figure 2). Of these, 70 (4.6%) died in the hospital, with 29 (1.9%) dying within 30 days of hospitalization (Table 1).

Table 2 shows the chemotherapeutic regimens administered to patients involved in this study, which were classified by their risk scores for acute IP exacerbations as proposed by Isoe et al. We noted that 10% of patients involved in this study had been administered chemotherapeutic regimens while having a risk score of 3, indicating a 30% or higher probability of developing an acute IP exacerbation (Table 2).

Factors related to in-hospital mortality

Factors related to in-hospital mortality for lung cancer treated with systemic chemotherapy were analyzed using the Cox proportional hazards model (Table 3). Univariate analysis revealed that poor respiratory condition on admission (Fletcher, Hugh-Jones scale 3–5), low ADL scores on admission (Barthel Index ≤90), platelet transfusion, and high-dose corticosteroid therapy were related to in-hospital mortalities following chemotherapy, and among these, high-dose corticosteroid therapy was an especially strong risk factor for in-hospital mortality (hazard ratio 3.56, 95% confidence interval 2.08–6.12, p < 0.001) following

### Table 1 Clinical characteristics of patients

| Total n (%) = 1524 (100) | Brinkmann Index |
|--------------------------|----------------|
| **Age (years) (median [range])** | **71.0 (34.0–91.0)** |
| 18–64 (%) | 392 (25.8) |
| 65–74 (%) | 698 (45.8) |
| ≥75 (%) | 434 (28.5) |
| **Sex** | |
| Male (%) | 1280 (84.0) |
| Female (%) | 244 (16.0) |
| **BMI (kg/m²) (mean ± SD)** | 22.5 ± 3.3 |
| <19 (%) | 161 (10.6) |
| 19–24 (%) | 1024 (67.2) |
| ≥25 (%) | 332 (21.8) |
| **Missing (%)** | 7 (0.5) |
| **F, H-J scale** | |
| 1–2 (%) | 1045 (68.6) |
| 3–5 (%) | 442 (29.0) |
| **Missing (%)** | 37 (2.4) |
| **ADL on admission** | |
| Independent (100–95) (%) | 1375 (90.2) |
| Dependent (≤90) (%) | 106 (7.0) |
| **Missing (%)** | 43 (2.8) |
| **Comorbidity** | |
| aCCI | |
| ≤3 (%) | 380 (24.9) |
| 4–5 (%) | 880 (57.7) |
| ≥6 (%) | 264 (17.3) |
| **Dementia (%)** | 168 (11.0) |
| **Collagen diseases (%)** | 106 (7.0) |
| **IPF (%)** | 150 (9.8) |

**Abbreviations:** aCCI, age-adjusted Charlson comorbidity index; ADL, activities of daily living; BMI, body mass index; F, H-J scale, Fletcher, Hugh-Jones scale; G-CSF, granulocyte colony-stimulating factor; IPF, idiopathic pulmonary fibrosis; IPI, idiopathic pulmonary fibrosis; LCNEC, large cell neuroendocrine carcinoma; NSCLC, non-small-cell lung carcinoma; platinum doublet, combination with platinum agents; platinum triplet, combination with platinum agents and other two anticancer agent; SCLC, small cell lung carcinoma; SD, standard deviation; TKI, tyrosine kinase inhibitor.

*a* Overlapping; more than two regimens of cytotoxic agents were used during one hospitalization.

*b* High-dose corticosteroids; methylprednisolone ≥500 mg/day following chemotherapy.
### Chemotherapeutic regimens administered classified by the risk for an acute interstitial pneumonia exacerbation

| Cytotoxic agents         | Risk score<sup>a</sup> | n   | NSCLC (n [%]) | SCLC (LCNEC) (n [%]) | Not otherwise specified (n [%]) | High-dose corticosteroid<sup>b</sup> use after chemotherapy (n) |
|--------------------------|------------------------|-----|---------------|----------------------|--------------------------------|---------------------------------------------------------------|
| CBDCA + PTX              | 1                      | 143 | 68 (467)      | 262 (17.2)           | 795 (53.2)                     | 1                                                            |
| CBDCA + PTX + Bev        | 1                      | 58  | 24 (467)      | 0                    | 34                             | 1                                                            |
| PTX                      | 1                      | 17  | 2 (262)       | 10                   | 5                              | 1                                                            |
| CBDCA + nab-PTX          | 1                      | 133 | 59 (795)      | 1                    | 73                             | 4                                                            |
| nab-PTX                  | 1                      | 17  | 9 (795)       | 0                    | 8                              | 2                                                            |
| CBDCA + S-1              | 1                      | 4   | 1 (133)       | 0                    | 3                              | 0                                                            |
| CBDCA + S-1              | 1                      | 49  | 26 (133)      | 0                    | 23                             | 1                                                            |
| S-1                      | 1                      | 34  | 22 (49)       | 1                    | 11                             | 2                                                            |
| CBDCA + VP-16            | 1                      | 83  | 0 (34)        | 35                   | 48                             | 2                                                            |
| CBDCA + VP-16            | 1                      | 262 | 3 (134)       | 138                  | 121                            | 3                                                            |
| VP-16                    | 1                      | 5   | 0 (262)       | 4                    | 1                              | 0                                                            |
| CDDP                     | 1                      | 10  | 7 (34)        | 0                    | 3                              | 0                                                            |
| CBDCA                    | 1                      | 1   | 1 (10)        | 0                    | 0                              | 0                                                            |
| CDDP + PEM               | 1                      | 50  | 25 (49)       | 0                    | 25                             | 2                                                            |
| CDDP + PEM + Bev         | 2                      | 23  | 8 (25)        | 0                    | 15                             | 0                                                            |
| CBDCA + PEM              | 2                      | 79  | 40 (23)       | 0                    | 39                             | 0                                                            |
| CBDCA + PEM + Bev        | 2                      | 59  | 23 (40)       | 0                    | 36                             | 0                                                            |
| PEM + Bev                | 2                      | 13  | 2 (23)        | 0                    | 11                             | 0                                                            |
| PEM                      | 2                      | 57  | 25 (23)       | 0                    | 32                             | 1                                                            |
| CDDP + DOC               | 2                      | 5   | 1 (57)        | 0                    | 4                              | 0                                                            |
| CBDCA + DOC              | 2                      | 7   | 3 (57)        | 0                    | 4                              | 0                                                            |
| DOC + Bev                | 2                      | 6   | 5 (3)         | 0                    | 1                              | 0                                                            |
| DOC                      | 2                      | 102 | 44 (3)        | 0                    | 58                             | 4                                                            |
| CDDP + VNR               | 2                      | 4   | 3 (102)       | 0                    | 1                              | 0                                                            |
| CBDCA + VNR              | 2                      | 2   | 1 (4)         | 0                    | 1                              | 0                                                            |
| VNR                      | 2                      | 42  | 20 (2)        | 0                    | 22                             | 1                                                            |
| NGT                      | 2                      | 5   | 0 (2)         | 23                   | 27                             | 1                                                            |
| Gefitinib                | 3                      | 6   | 11 (50)       | 0                    | 15                             | 1                                                            |
| Erlotinib                | 3                      | 13  | 7 (11)        | 0                    | 6                              | 0                                                            |
| Afatinib                 | 3                      | 11  | 8 (6)         | 0                    | 3                              | 0                                                            |
| Crizotinib               | 3                      | 1   | 0 (1)         | 0                    | 1                              | 0                                                            |
| CDDP + CPT-11            | 3                      | 25  | 0 (1)         | 2                    | 23                             | 0                                                            |
| CBDCA + CPT-11           | 3                      | 14  | 0 (25)        | 7                    | 7                              | 0                                                            |
| CPT-11                   | 3                      | 1   | 1 (14)        | 3                    | 7                              | 0                                                            |
| CDDP + GEM + Bev         | 3                      | 2   | 0 (14)        | 0                    | 2                              | 0                                                            |
| GEM + VNR                | 3                      | 5   | 1 (2)         | 0                    | 4                              | 0                                                            |
| GEM                      | 3                      | 7   | 4 (5)         | 0                    | 3                              | 0                                                            |
| AMR                      | 3                      | 5   | 1 (1)         | 19                   | 31                             | 0                                                            |
| Overlapping<sup>c</sup>  | –                      | 40  | 12 (5)        | 2                    | 21                             | 4                                                            |

**Abbreviations:** AMR, amrubicin; Bev, bevacizumab; CBDCA, carboplatin; CDDP, cisplatin; CPT-11, irinotecan; DOC, docetaxel; GEM, gemcitabine; LCNEC, large cell neuroendocrine carcinoma; nab-PTX, nanoparticle albumin-bound paclitaxel; NGT, nogitecan; NSCLC, non-small-cell lung carcinoma; PEM, pemetrexed; PTX, paclitaxel; SCLC, small-cell lung carcinoma; VNR, vinorelbine; VP-16, etoposide.

<sup>a</sup>An acute exacerbation frequency of 30%, 11–29%, and <10% was classified as high (3 points), moderate (2 points), and low risk (1 point), respectively.

<sup>b</sup>High-dose corticosteroids; methylprednisolone ≥500 mg/day.

<sup>c</sup>Overlapping; more than two regimens of cytotoxic agents were used during one hospitalization.
| TABLE 3 | Variables related to hospitalization death analyzed using the Cox proportional hazard model |
|---------|---------------------------------------------------------------------------------------|
|         | Total n (%) = 1524 (100) | Univariate analysis with Cox’s proportional hazard model | Hazard ratio (95% CI) | p value | Multivariable logistic analysis with Cox’s proportional hazard model | Hazard ratio (95% CI) | p value |
|         |                             | Hazard ratio (95% CI) | p value |                             | Hazard ratio (95% CI) | p value |
| Age (years) | | | | | | |
| 18–64 (%) | 392 (25.8) | 1 | | | | |
| 65–74 (%) | 698 (45.8) | 1.3 (0.70–2.43) | 0.407 | 1.8 (0.91–3.58) | 0.093 |
| ≥75 (%) | 434 (28.5) | 1.29 (0.65–2.55) | 0.471 | 1.56 (0.75–3.23) | 0.23 |
| Male | 1280 (84.0) | 1.25 (0.57–2.76) | 0.574 | | | |
| BMI (kg/m²) | | | | | | |
| <19 (%) | 161 (10.6) | 1.34 (0.74–2.43) | 0.333 | | | |
| 19–24.9 (%) | 1024 (67.2) | 1 | | | | |
| ≥25 (%) | 332 (21.8) | 0.72 (0.36–1.43) | 0.343 | | | |
| Brinkmann index | | | | | | |
| <400 (%) | 458 (30.1) | 1 | | | | |
| ≥400 (%) | 1066 (69.9) | 0.9 (0.55–1.48) | 0.679 | | | |
| F, H-J scale | | | | | | |
| 1–2 (%) | 1045 (68.6) | 1 | | | | |
| 3–5 (%) | 442 (29.0) | 1.81 (1.08–3.04) | 0.025 | 1.43 (0.82–2.50) | 0.21 |
| ADL on admission | | | | | | |
| Independent (100–95) (%) | 1375 (90.2) | 1 | | | | |
| Dependent (≤90) (%) | 106 (7.0) | 3.12 (1.82–5.35) | <0.001 | 2.26 (1.24–4.12) | 0.008 |
| Comorbidity | | | | | | |
| aCCI | | | | | | |
| ≤3 | 380 (24.9) | 1 | | | | |
| 4–5 | 880 (57.7) | 0.96 (0.53–1.74) | 0.905 | | | |
| ≥6 | 264 (17.3) | 0.81 (0.36–1.81) | 0.605 | | | |
| With dementia (%) | 168 (11.0) | 1.43 (0.52–3.97) | 0.487 | | | |
| Use of immunosuppression drugs (%) | 18 (1.2) | 1.15 (0.36–3.71) | 0.818 | | | |
| Corticosteroid use before chemotherapy (%) | 124 (8.1) | 1.7 (0.91–3.15) | 0.094 | | | |
| Complications of collagen diseases (%) | 106 (7.0) | 0.84 (0.30–2.31) | 0.735 | | | |
| Diagnosis of IPF (%) | 150 (9.8) | 0.65 (0.28–1.52) | 0.32 | | | |
| Use of antifibrotic agent (%) | 16 (1.0) | 1.16 (0.28–4.79) | 0.838 | | | |
| Supportive therapy (%) | | | | | | |
| Use of G-CSF (%) | 351 (23.0) | 0.94 (0.58–1.54) | 0.816 | | | |
| Red blood cell transfusion (%) | 34 (2.2) | 1.22 (0.52–2.85) | 0.645 | | | |
| Platelet transfusion (%) | 28 (1.8) | 2.27 (1.15–4.50) | 0.019 | 1.7 (0.74–3.93) | 0.21 |
| Hospital volume (per-year) | | | | | | |
| ≥7 | 866 (56.8) | 1.09 (0.67–1.76) | 0.741 | | | |
| <7 | 658 (43.2) | 1 | | | | |
| High-dose corticosteroid use after chemotherapy (%) | 31 (2.0) | 3.56 (2.08–6.12) | <0.001 | 2.62 (1.44–4.77) | 0.002 |
| Histology | | | | | | |
| NSCLC (%) | 467 (30.6) | 0.75 (0.42–1.35) | 0.341 | | | |
| SCLC・LCNEC (%) | 262 (17.2) | 1.02 (0.54–1.91) | 0.957 | | | |
| Not otherwise specified (%) | 795 (52.2) | 1 | | | | |

**Abbreviations:** aCCI, age-adjusted Charlson comorbidity index; ADL, activities of daily living; BMI, body mass index; F, H-J scale, Fletcher, Hugh-Jones scale; G-CSF, granulocyte-colony stimulating factor; IPF, idiopathic pulmonary fibrosis; IPF, idiopathic pulmonary fibrosis; LCNEC, large cell neuroendocrine carcinoma; NSCLC, non-small-cell lung carcinoma; platinum doublet, combination with platinum agents; platinum triplet, combination with platinum agents and other two anticancer agent; SCLC, small-cell lung carcinoma; SD, standard deviation; TKI, tyrosine kinase inhibitor.
| Case | Age (years) | Sex | Histology | DPC name for interstitial pneumonia | Cytotoxic agents | F, H-J scale | ADL | Comorbidities (based on ICD-10) | Outcome |
|------|-------------|-----|-----------|-----------------------------------|-----------------|-------------|-----|---------------------------------|---------|
| 1    | 79          | Male | Not otherwise specified | IP                          | CBDCA + VP-16   | 3           | Independent | Emphysema, common iliac artery sclerosis, pleural effusion | Death   |
| 2    | 67          | Male | SCLC      | IP                          | Overlapping     | 3           | Independent | Hiatal hemia, reflux esophagitis | Death   |
| 3    | 67          | Male | Adeno     | IPF                        | nab-PTX         | 2           | Dependent   | None             | Death   |
| 4    | 63          | Male | Not otherwise specified | IP                          | Overlapping     | 1           | Independent | Seborrheic dermatitis, pimples vulgaris | Survival |
| 5    | 66          | Male | SCLC      | IP                          | NGT             | 4           | Dependent   | Hypertension, chronic gastritis, iron deficiency anemia, hyperlipidemia, postherpetic neuralgia, steroid diabetes, benign prostatic hyperplasia | Survival |
| 6    | 71          | Male | Sq        | IP                          | CBDCA + nab-PTX | 4           | Independent | Chronic obstructive pulmonary disease | Death   |
| 7    | 70          | Male | Not otherwise specified | IP                          | Overlapping     | 5           | Missing     | Hypertension, constipation         | Death   |
| 8    | 64          | Male | Adeno     | UIP                        | CDDP + PEM      | 1           | Independent | Hypoxemia, constipation, hemorrhagic gastric ulcer, febrile neutropenia | Death   |
| 9    | 78          | Male | Not otherwise specified | IP                          | CDDP + VP-16    | 1           | Dependent   | Hypoxemia, constipation, hemorrhagic gastric ulcer, febrile neutropenia | Death   |
| 10   | 81          | Male | Not otherwise specified | IP                          | PEM             | 2           | Independent | Paroxysmal atrial fibrillation, old cerebral infarction, emphysema, steroid diabetes, reflux esophagitis, disuse syndrome, urinary infection | Survival |
| 11   | 70          | Male | Not otherwise specified | AIP                        | CBDCA + PTX + Bev | 5           | Dependent   | Type 2 diabetes, neutropenia, anemia, catheter infection, sepsis | Death   |
| 12   | 72          | Male | NSCLC     | IP                          | CBDCA + nab-PTX | Missing     | Missing     | Acute renal failure, hyperkalemia, perforated gastric ulcer | Death   |
| 13   | 65          | Male | Not otherwise specified | UIP                        | CDDP + VP-16    | 5           | Independent | None             | Death   |
| 14   | 65          | Male | Not otherwise specified | IP                          | CBDCA + nab-PTX | 5           | Independent | Weakness of limbs         | Death   |
| 15   | 70          | Male | Not otherwise specified | IIP                        | CBDCA + PTX     | 3           | Independent | Reflux esophagitis          | Survival |
| 16   | 70          | Male | Adeno     | IP                          | S-1             | 5           | Dependent   | Chronic respiratory failure, chronic obstructive pulmonary disease, pneumonia, lumbar compression fracture, asthma, thromboembolism | Death   |
| 17   | 66          | Male | Not otherwise specified | IP                          | DOC             | 2           | Independent | Reflux esophagitis          | Death   |
| 18   | 81          | Male | Adeno     | IP                          | S-1             | 3           | Dependent   | Pleural Effusion             | Survival |
| 19   | 74          | Male | Adeno     | IP                          | DOC             | Missing     | Missing     | Type 2 diabetes, angina, rheumatoid arthritis, neutropenia, hypoalbuminemia | Death   |

(Continues)
| Case | Age (years) | Sex | Histology                  | DPC name for interstitial pneumonia | Cytotoxic agents  | F, H-J scale | ADL         | Comorbidities (based on ICD-10)                                                                 | Outcome |
|------|-------------|-----|----------------------------|------------------------------------|-------------------|--------------|-------------|-----------------------------------------------------------|---------|
| 20   | 65          | Male| Not otherwise specified    | IIP                                | CBDCA + VP-16     | 3            | Independent  | Emphysema, pleural effusion, chronic respiratory failure, insomnia, constipation, suspected brain contusion   | Death   |
| 21   | 67          | Male| Adeno                      | IP                                 | DOC               | 1            | Independent  | Old cerebral infarction, hypertension, type 2 diabetes     | Survival|
| 22   | 70          | Male| Not otherwise specified    | AE-IP                              | nab-PTX           | 5            | Independent  | Steroid diabetes, hypertension, reflux esophagitis, paroxysmal atrial fibrillation, pneumocystis pneumonia, pleural effusion, chronic heart failure | Death   |
| 23   | 64          | Male| Not otherwise specified    | IP                                 | CBDCA + S-1       | 1            | Missing     | None                                                      |         |
| 24   | 60          | Male| Not otherwise specified    | IP                                 | CDDP + PEM        | 3            | Independent  | Postoperative cardio cancer, fatty liver, hypertension, vomiting associated with chemotherapy, insomnia, pancytopenia   | Death   |
| 25   | 77          | Female| SCLC                      | IP                                 | CBDCA + VP-16     | 4            | Independent  | Type 2 diabetes, hypertension, pneumonia, pleural effusion, suspected tuberculosis                          | Death   |
| 26   | 65          | Male| Sq                         | IP                                 | CBDCA + nab-PTX   | 5            | Dependent    | Hypertension, chronic respiratory failure, hemoptysis, hyperlipidemia, chronic pharyngitis, reflux esophagitis, suppured cyst | Survival|
| 27   | 66          | Male| Adeno                      | IP                                 | Gefitinib         | 3            | Independent  | Type 2 diabetes, peripheral neuropathic pain, osteoporosis                                               | Survival|
| 28   | 62          | Male| Not otherwise specified    | IP                                 | VNR               | 3            | Dependent    | Chronic renal failure, symptomatological epilepsy, constipation, phlebitis, bacterial pneumonia, dysphagia | Death   |
| 29   | 76          | Male| Sq                         | IIP                                | DOC               | 2            | Missing      | Hypertension, vomiting associated with chemotherapy, chronic gastritis, acute pancreatitis, ringworm on the face, neutropenia | Survival|
| 30   | 74          | Male| SCLC                       | IP                                 | PTX               | 2            | Independent  | Type 2 diabetes                                                                                             | Survival|
| 31   | 62          | Male| Not otherwise specified    | IP                                 | Overlappinga      | Missing      | Missing      | IgA nephropathy, type 2 diabetes                                                                              | Death   |

Abbreviations: Adeno, adenocarcinoma; AE-IP, acute exacerbation of interstitial pneumonia; AIP, acute interstitial pneumonia; Bev, bevacizumab; CBDCA, carboplatin; CDDP, cisplatin; DOC, docetaxel; IgA, immunoglobulin A; IIP, idiopathic interstitial pneumonia; IP, interstitial pneumonia or diffuse interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; nab-PTX, nanoparticle albumin-bound paclitaxel; PEM, pemetrexed; PTX, paclitaxel; SCLC, small-cell lung carcinoma; Sq, squamous carcinoma; UIP, usual interstitial pneumonia; VNR, vinorelbine; VP-16, etoposide.

a Overlapping: more than two regimens of cytotoxic agents were used during one hospitalization.
Multivariate analysis showed that a low ADL score and high-dose corticosteroid therapy were associated with in-hospital mortality. None of the 31 patients who received high-dose corticosteroid therapy for acute IP exacerbations had any other indications for corticosteroid use (Table 4).

**Survival time analysis**

Using the Kaplan–Meier method, significant factors related to shorter survival times were determined. The factors identified were a low ADL score on admission and treatment with high-dose corticosteroids.
with high-dose corticosteroids (Figure 3). Twenty-one of the 31 patients (67.7%) treated with high-dose corticosteroid therapy following chemotherapy died in the hospital.

**DISCUSSION**

This study found that 4.6% (70/1524) of lung cancer patients with IP died in the hospital while being administered systemic chemotherapy, and 1.9% (29/1524) specifically died within 30 days of admission. In addition, a low ADL score on admission was associated with a higher mortality risk from systemic chemotherapy.

In this study, we found that acute exacerbations of IP were significantly associated with in-hospital mortality following chemotherapy. High-dose corticosteroid therapy is often used to treat acute IP exacerbations; the 31 patients who were treated with high-dose corticosteroid therapy had no indications for corticosteroid use other than IP exacerbations (Table 4). More than half of the lung cancer patients with IP who underwent high-dose corticosteroid therapy following systemic chemotherapy died in the hospital. A median survival time of 55 days (31–69 days) was identified. This was similar to the reported 3-month median survival time of patients with IPF exacerbations, with IPF patients having a fatality rate of 50%.\(^{8–10}\) Compared to the reported probability of 5%–15%\(^ {14–16}\) for developing acute IP exacerbations from systemic chemotherapy, our study demonstrated that only 2% of lung cancer patients possibly developed an acute IP exacerbation, as evidenced by their receipt of high-dose corticosteroids. This might be because the clinicians shifted to palliative care to avoid the risk of developing acute IP exacerbations in patients receiving late-line chemotherapy or those with poor PS with a limited prognosis for advanced lung cancer.

The risk of acute IP exacerbation varies depending on the chemotherapeutic regimen used, and some anticancer drugs are contraindicated in patients with IP. The chemotherapeutic regimens involved in this study were similar to those in a previous study that also involved lung cancer patients with IP. The aforementioned study\(^ {16}\) mainly used platinum-based doublet regimens consisting of paclitaxel (PTX) and nab-PTX (nanoparticle albumin-bound PTX) for non-small-cell lung cancer and etoposide-based regimens for small cell lung cancer. A lower risk for acute IP exacerbations has been reported in patients receiving PTX and nab-PTX for non-small-cell lung cancer,\(^ {6,17}\) with these patients only having a less than 10% chance of developing an IP exacerbation as their risk scores\(^ {12}\) were only 1. These drugs were used in about half of the patients (53.5%) involved in our study.

Treatment of lung cancer patients with IP involves many clinically controversial aspects of note, such as proper appreciation of aggressive anticancer treatment with favorable regimens in each patient considering risk factors. Previous studies enrolled approximately several hundred patients,\(^ {6,7,11,12,16}\) and our research was a national survey of more than 1500 lung cancer patients with IP. In addition, since the survey used data from across Japan, the selection bias might be lower than that in previous studies, reflecting better applicability in clinical practice. Although the risk of chemotherapy for patients with low ADL scores (poor PS) is previously reported, no studies have yet explored the risk estimate in lung cancer patients with IP. Considering that lung cancer patients with IP usually have worse prognoses than those without IP, clinicians should be exceedingly cautious about the adequacy of treatment for lung cancer patients with IP and low ADL scores.

This study had several limitations. First, the diagnoses retrieved from the DPC database did not reflect the different pathological types of IP. Cases with UIP pattern on chest computed tomography are shown to have a high risk of acute exacerbations of IP.\(^ {11}\) Most cases (71.2%) in the present study had unclassifiable disease name codes (e.g. ICD-10 J84.1 Interstitial pneumonia, J84.1 Diffuse interstitial pneumonia) in the DPC coding and unclassifiable patterns of IP. Second, laboratory results from blood, imaging, and respiratory function tests were not available, and thus the risk factors for acute IP exacerbations could not be sufficiently evaluated. Third, the DPC did not store data on rehospitalization or outpatient chemotherapy cases. Fourth, it was not possible to identify if a patient received first- or second-line chemotherapy based solely on the data stored in the DPC. Finally, the use of immune checkpoint inhibitors was not adequately assessed in our study because a significant number of patients who had been administered these agents were not included in the target period.

In conclusion, when systemic chemotherapy is administered to lung cancer patients with IP, patients with a low ADL score on admission are at increased risk of in-hospital mortality. Thus, clinicians should be careful in the introduction and selection of chemotherapeutic regimens for these patients. Furthermore, we found that treatment of acute exacerbations of IP with high-dose corticosteroids was clearly associated with in-hospital mortality when compared with other risk factors such as age and complications.

**CONFLICT OF INTEREST**

The authors have no conflict of interest.

**ORCID**

Kei Yamasaki
https://orcid.org/0000-0003-1876-3287

**REFERENCES**

1. Ryerson CJ, Cottin V, Brown KK, Collard HR. Acute exacerbation of idiopathic pulmonary fibrosis: shifting the paradigm. Eur Respir J. 2015;46:512–20.

2. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur Respir J. 2011;37:356–63.

3. Collard HR, Yow E, Richeldi L, Anstrom KJ, Glazer C, for the IPFnet Investigators. Suspected acute exacerbation of idiopathic pulmonary fibrosis as an outcome measure in clinical trials. Respir Res. 2013;14:73.

4. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis: a population-based cohort study. Am J Respir Crit Care Med. 2000;161:5–83.
