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ORIGINAL ARTICLE

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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

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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 IIIB 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 similar, 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 IP[6,7]; however, the specific protective and risk factors in these patients are not yet completely understood. Besides known 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 predict acute IPF exacerbations using a patient's smoking history, chemotherapeutic medication history, and diffusing capacity of the lung for carbon monoxide has been proposed[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 examination 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 comorbidities 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 cigarettes 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 dyspnea 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 cancer as defined by the Union for International Cancer Control Tumor-Nodes-Metastases (UICC TNM) 6th and 7th editions 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 pneumonia if an ICD-10 code of J84, J84.1, or J84.9 (other interstitial 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 exacerbations 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 methylprednisolone 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 mortality. 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 survival, 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 univariate 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]

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

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

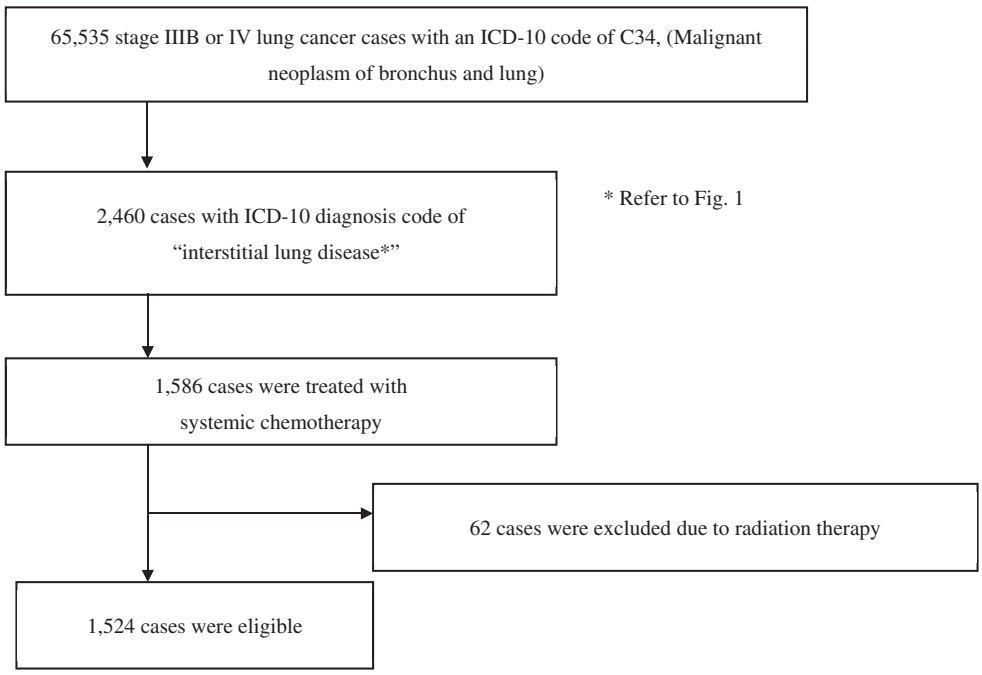


FIGURE 2 Patient selection flow chart

RESULTS

Patient background

Among the 65 535 stage IIIB/IV lung cancer patients treated with chemotherapy, 1586 had concurrent IP and were receiving systemic chemotherapy and 62 were excluded as they had received radiation therapy, leaving 1524 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 Isobe et al.[12] 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)			
Age (years) (median [range])	**71.0 (34.0–91.0)**	**Brinkmann Index**	
18–64 (%)	392 (25.8)	<400 (%)	458 (30.1)
65–74 (%)	698 (45.8)	≥400 (%)	1066 (69.9)
≥75 (%)	434 (28.5)	Therapy of interstitial pneumonia	
Sex		Antifibrotic agent (%)	16 (1.0)
Male (%)	1280 (84.0)	Immunosuppression drugs (%)	18 (1.2)
Female (%)	244 (16.0)	Corticosteroids before chemotherapy (%)	124 (8.1)
BMI (kg/m^2) (mean ± SD)	22.5 ± 3.3	Supportive therapy	
<19 (%)	161 (10.6)	G-CSF (%)	351 (23.0)
19–24 (%)	1024 (67.2)	Red blood cell transfusion (%)	34 (2.2)
≥25 (%)	332 (21.8)	Platelet transfusion (%)	28 (1.8)
Missing (%)	7 (0.5)	Cytotoxic agents	
F, H-J scale		Monotherapy (%)	393 (25.8)
1–2 (%)	1045(68.6)	Platinum doublet (%)	863 (56.6)
3–5 (%)	442 (29.0)	Platinum triplet (%)	142 (9.3)
Missing (%)	37 (2.4)	Other combination therapy (%)	24 (1.6)
ADL on admission		TKI (%)	51 (3.3)
Independent (100–95) (%)	1375 (90.2)	Platinum monotherapy (%)	11 (0.7)
Dependent (≤90) (%)	106 (7.0)	Overlapping[a] (%)	40 (2.6)
Missing (%)	43 (2.8)	Histology	
Comorbidity		NSCLC (%)	467 (30.6)
aCCI		SCLC・LCNEC (%)	262 (17.2)
≤3 (%)	380 (24.9)	Not otherwise specified (%)	795 (52.2)
4–5 (%)	880 (57.7)	High-dose Corticosteroids[b] use after chemotherapy (%)	31 (2.0)
≥6 (%)	264 (17.3)	Hospital volume (per-year) (median [range])	7.0 [1.0–44.0]
Dementia (%)	168 (11.0)	≥7	866 (56.8)
Collagen diseases (%)	106 (7.0)	<7	658 (43.2)
IPF (%)	150 (9.8)	In-hospital death (%)	70 (4.6)

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.

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

[b]High-dose corticosteroids; methylprednisolone ≥500 mg/day following chemotherapy.

TABLE 2 Chemotherapeutic regimens administered classified by the risk for an acute interstitial pneumonia exacerbation

			Histology			
Cytotoxic agents	**Risk score[a]**	**n**	**NSCLC (*n* [%]) 467 (30.6)**	**SCLC· LCNEC (*n* [%]) 262 (17.2)**	**Not otherwise specified (*n* [%]) 795 (53.2)**	**High-dose corticosteroid[b] use after chemotherapy (*n*)**
CBDCA+PTX	1	143	68	9	66	1
CBDCA+PTX+Bev	1	58	24	0	34	1
PTX	1	17	2	10	5	1
CBDCA+nab-PTX	1	133	59	1	73	4
nab-PTX	1	17	9	0	8	2
CDDP+S-1	1	4	1	0	3	0
CBDCA+S-1	1	49	26	0	23	1
S-1	1	34	22	1	11	2
CDDP+VP-16	1	83	0	35	48	2
CBDCA+VP-16	1	262	3	138	121	3
VP-16	1	5	0	4	1	0
CDDP	1	10	7	0	3	0
CBDCA	1	1	1	0	0	0
CDDP+PEM	2	50	25	0	25	2
CDDP+PEM+Bev	2	23	8	0	15	0
CBDCA+PEM	2	79	40	0	39	0
CBDCA+PEM+Bev	2	59	23	0	36	0
PEM+Bev	2	13	2	0	11	0
PEM	2	57	25	0	32	1
CDDP+DOC	2	5	1	0	4	0
CBDCA+DOC	2	7	3	0	4	0
DOC+Bev	2	6	5	0	1	0
DOC	2	102	44	0	58	4
CDDP+VNR	2	4	3	0	1	0
CBDCA+VNR	2	2	1	0	1	0
VNR	2	42	20	0	22	1
NGT	2	50	0	23	27	1
Gefitinib	3	26	11	0	15	1
Erlotinib	3	13	7	0	6	0
Afatinib	3	11	8	0	3	0
Crizotinib	3	1	0	0	1	0
CDDP+CPT-11	3	25	0	2	23	0
CBDCA+CPT-11	3	14	0	7	7	0
CPT-11	3	11	1	3	7	0
CDDP+GEM+Bev	3	2	0	0	2	0
GEM+VNR	3	5	1	0	4	0
GEM	3	7	4	0	3	0
AMR	3	51	1	19	31	0
Overlapping[c]	–	40	12	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.

[a]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.

[b]High-dose corticosteroids; methylprednisolone ≥500 mg/day.

[c]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	Univariate analysis with Cox's proportional hazard model		Multivariable logistic analysis with Cox's proportional hazard model	
	n (%) = 1524 (100)	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/m^2)					
<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		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		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.

TABLE 4 Characteristics and comorbidities of patients who used high-dose corticosteroids after chemotherapy

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 hernia, 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	Hypertension, asthma, ulceration of nasal septum	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)

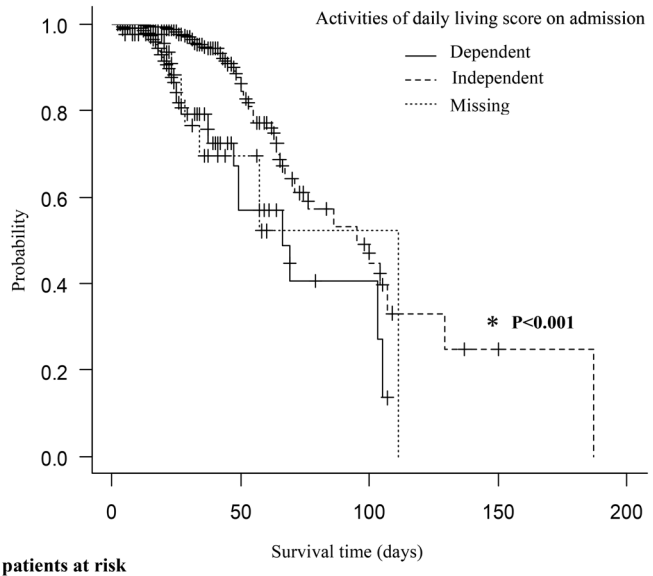
TABLE 4 (Continued)

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	Death
24	60	Male	Not otherwise specified	IP	CDDP+PEM	3	Independent	Postoperative cardia 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, suppurated 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	Overlapping[a]	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.

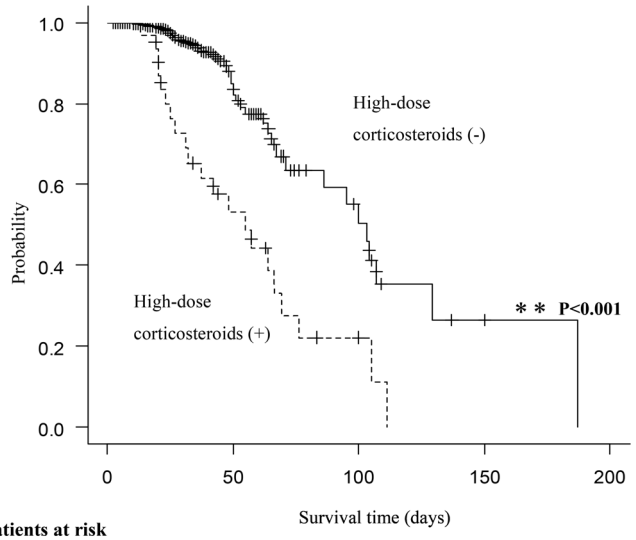
a



Number of patients at risk				
Dependent	106	11	3	0
Independent	375	54	11	2
Missing	43	6	1	0

	n	Number of deaths (%)	Median survival (95% CI)
Dependent	106	21(19.8)	66(47-105)
Independent	1375	41(3.0)	95(67-129)
Missing	43	8(18.6)	111(34-NA)

b



Number of patients at risk					
High-dose	(-)	1493	59	12	2
corticosteroids	(+)	31	12	3	0

		n	Number of deaths (%)	Median survival (95% CI)
High-dose	(-)	1493	49 (3.3)	103 (71-129)
corticosteroids	(+)	31	21 (67.7)	55 (31-69)

FIGURE 3 Kaplan–Meier plots of survival probability from the time of admission based on the patients' ability to performed activities of daily living (a) and whether or not they were treated with high-dose corticosteroids (methylprednisolone ≥ 500 mg/day) (b)

chemotherapy. 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 (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.

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