ORIGINAL ARTICLE

Cancer Science WILEY

Gemcitabine plus nab-paclitaxel for pancreatic cancer and interstitial lung disease: A nationwide longitudinal study

Kei Saito[1,2] | Nobuaki Michihata[3] | Tsuyoshi Hamada[1,4] | Taisuke Jo[3,5] | Hiroki Matsui[6] | Kiyohide Fushimi[7] | Yousuke Nakai[1,8] | Hideo Yasunaga[6] | Mitsuhiro Fujishiro[1]

[1]Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Nihon University School of Medicine, Tokyo, Japan

[3]Department of Health Services Research, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[4]Department of Hepato-Biliary-Pancreatic Medicine, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

[5]Department of Respiratory Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[6]Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan

[7]Department of Health Informatics and Policy, Graduate School of Medicine, Tokyo Medical and Dental University, Tokyo, Japan

[8]Department of Endoscopy and Endoscopic Surgery, The University of Tokyo Hospital, Tokyo, Japan

Correspondence
Tsuyoshi Hamada, Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo City, Tokyo 113-8655, Japan.
Email: hamada-tky@umin.ac.jp

Abstract

Interstitial lung disease (ILD) is an adverse event associated with gemcitabine administration. Gemcitabine plus nab-paclitaxel, which is now a first-line chemotherapy regimen for pancreatic cancer (PC), may increase the risk of ILD; however, large-scale clinical data on this are limited. Thus, this study aimed to elucidate the incidence and risk factors of ILD in patients with PC receiving gemcitabine plus nab-paclitaxel. Through the Diagnosis Procedure Combination database, a Japanese nationwide in-patient database with outpatient data, we identified consecutive patients with PC who received gemcitabine-based chemotherapy between July 2010 and March 2019 at 205 hospitals. Competing-risk analysis was used to examine the cumulative incidence and risk factors of ILD. Among the 6163 patients who received gemcitabine plus nab-paclitaxel, we documented 168 patients (2.7%) who developed ILD with cumulative incidence rates (95% confidence intervals [CIs]) of 2.0% (1.6%–2.4%), 2.7% (2.2%–3.1%), and 3.1% (2.6%–3.6%) at 3, 6, and 12 months, respectively. Compared with patients with PC who received gemcitabine monotherapy, those who received gemcitabine plus nab-paclitaxel had an adjusted subdistribution hazard ratio (SHR) for ILD of 1.93 (95% CI: 1.51–2.47). Older age was associated with a high risk of ILD

in patients receiving gemcitabine plus nab-paclitaxel (adjusted SHR comparing ≥75 to ≤74 years, 1.61; 95% CI: 1.16–2.24). In conclusion, this study demonstrated the clinical course of gemcitabine plus nab-paclitaxel-associated ILD in patients with PC. When gemcitabine plus nab-paclitaxel is administered to elderly patients with PC, symptoms associated with ILD must be monitored.

KEYWORDS
gemcitabine, interstitial lung disease, nab-paclitaxel, pancreatic cancer

1 | INTRODUCTION

Gemcitabine is a standard chemotherapeutic agent with a tolerable toxic property and an effective anti-tumor effect on PC.[1–3] However, pulmonary toxicity is one of its recognized adverse events, which potentially results in substantial morbidity and mortality.[4,5] The clinical presentations of pulmonary toxicity that were associated with gemcitabine range from mild self-limiting symptoms (e.g., cough, dyspnea) to severe potentially fatal pulmonary disorders requiring intensive in-hospital care (e.g., acute respiratory distress syndrome).[6] Severe pulmonary toxicity that is associated with gemcitabine typically develops as ILD based on inflammatory and fibrotic reactions in the parenchymal lung alveolar regions.

The anti-tumor effects of gemcitabine-based chemotherapy regimens, which consist of gemcitabine combined with cytotoxic or molecular-targeted agents, on PC have been further investigated.[7,8] Since a clinical randomized trial demonstrated that gemcitabine plus nab-paclitaxel has better tumor-suppressing properties compared with gemcitabine monotherapy in patients with unresectable PC,[9] gemcitabine plus nab-paclitaxel has been administered as one of the first-line regimens for this population.[9–12] Nab-paclitaxel is a solvent-free formulation of the chemotherapeutic agent, paclitaxel, that was initially developed to mitigate the toxicity associated with the solvent used and potentially enhance anti-tumor effects.[6,13] However, nab-paclitaxel administration may predispose the patients to the risk of ILD with a reported incidence rate of approximately 2%–10%.[14–17] Due to the lack of large-scale data on the head-to-head comparison between gemcitabine with and without nab-paclitaxel, whether the addition of nab-paclitaxel to gemcitabine elevates the risk of ILD is unknown. A large sample of cases is required to evaluate the incidence and risk factors of the relatively rare adverse event.[14–17]

Therefore, to address these clinical questions, we utilized a nationwide administrative database with outpatient data in Japan and conducted a retrospective population-based cohort study to compare the incidence of ILD between patients with PC who were administered with gemcitabine plus nab-paclitaxel and other gemcitabine-based chemotherapy regimens. We additionally examined the risk factors for ILD in patients with PC who were administered gemcitabine plus nab-paclitaxel.

2 | METHODS

2.1 | Study population

The DPC database, which is a nationwide administrative database of inpatient care in Japan that includes data on admission/discharge abstracts and administrative claims, was utilized.[18–20] Data on approximately 7 million inpatients were collected from >1000 hospitals throughout Japan in 2020. The data on inpatient care included main diagnoses, comorbidities identified at admission, and complications observed during hospitalizations, which were recorded according to the ICD-10 codes. The database also contains detailed clinical information on the Union for International Cancer Control TNM classification for cases with newly diagnosed cancer, smoking status based on the Brinkman index (number of cigarettes per day multiplied by smoking years), Barthel Index for the activities of daily living (0–100 points with higher scores indicating higher activity levels),[21] medications, interventional/surgical procedures (indexed by the Japanese original codes), and discharge status, including in-hospital mortality. Data on outpatients have been collected since 2010 from approximately 350 hospitals that also participated in inpatient data collection. Data on outpatient care included dates of outpatient clinic visits, procedures, and medications including intravenous and oral chemotherapeutic agents.

Adult patients (≥20 years old) who were admitted to any of the hospitals that participated in the outpatient data collection with a principal diagnosis of PC (ICD-10 codes: C25.0–25.3 and C25.7–25.9) were identified through the DPC database. We included patients who started receiving gemcitabine plus nab-paclitaxel or other gemcitabine-based chemotherapy regimens for PC between July 1, 2010 and March 31, 2019. We excluded patients with multiple cancer types or who were receiving other gemcitabine combination regimens (i.e., gemcitabine plus S-1 or gemcitabine plus erlotinib). In addition, we excluded patients having concomitant ILD at the time of gemcitabine-based chemotherapy initiation.

This study was approved by the institutional review board of The University of Tokyo (Tokyo, Japan; approval number, #3501-(5) [May 19, 2021]). The requirement for patients' written informed consent was waived because of the anonymity of the used data.
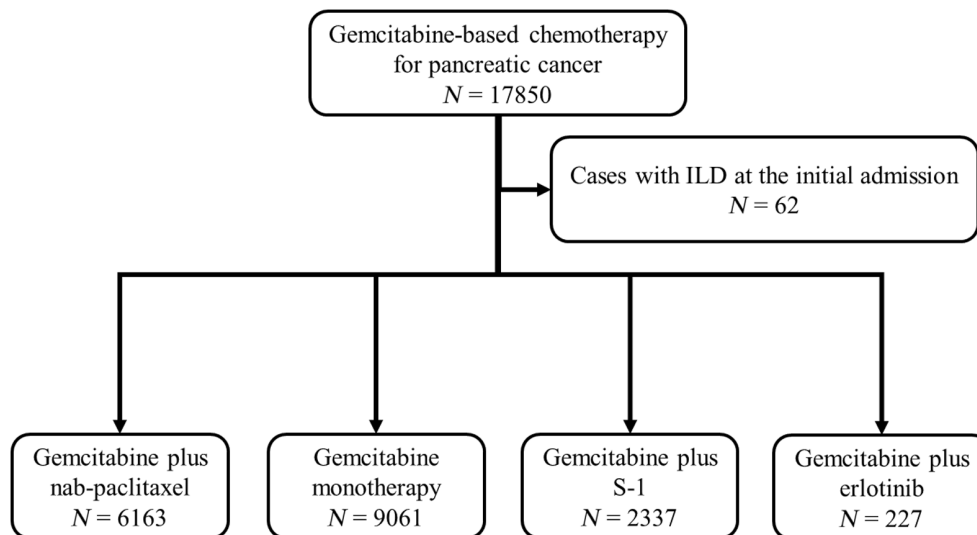
FIGURE 1 Flowchart of the selection of patients with pancreatic cancer receiving gemcitabine plus nab-paclitaxel or other gemcitabine-based chemotherapy regimens.

2.2 | Ascertainment of ILD cases

The primary outcome of this study was the development of ILD following gemcitabine-based chemotherapy that required hospitalization. ILD was defined according to the following ICD-10 codes: J70.2 (acute drug-induced interstitial lung disorders), J70.3 (chronic drug-induced interstitial lung disorders), J70.4 (drug-induced interstitial lung disorders, unspecified), J84.1 (other interstitial pulmonary diseases with fibrosis), and J84.9 (interstitial pulmonary disease, unspecified). Patients who were hospitalized for ILD were identified based on information on the ICD-10 codes at the index and all subsequent admissions.

2.3 | Definitions of other variables

Each ICD-10 code of comorbidity was converted to a score, and the sum was used to calculate the CCI based on Quan's algorithm.[22] BMI was calculated and classified into three categories (<25, 25–30, and >30 kg/m²). The ICD-10 codes were used to define COPD (J43), chronic lower respiratory tract infection (J40–J42 and J44), chronic renal failure (N18), liver cirrhosis (K74), and arrhythmia (I490–I495, I498, and I499).

2.4 | Statistical analysis

Time to ILD was defined as the period from the initiation of gemcitabine-based chemotherapy to hospitalization due to ILD, administration of subsequent chemotherapy, last follow-up, or death, whichever came first. When ILD occurred during the initial hospitalization, the date of ILD development was defined as the date of discharge during the corresponding hospitalization. When ILD was documented in subsequent hospitalizations, the date of ILD development was defined as the date of admission due to ILD. Cumulative incidences of ILD were calculated using a competing-risk analysis, in which the initiation of a subsequent

chemotherapy regimen and death were treated as competing-risk events and were compared using Gray's test.[23] Through the competing risks proportional hazard regression model with adjustment for potential confounders,[24] we calculated SHRs and 95% CIs for risk of ILD development comparing gemcitabine plus nab-paclitaxel to other gemcitabine-based chemotherapy regimens. Univariable analysis was conducted for each of the following variables: age (≤74 vs. ≥75 years), sex (female vs. male), the Barthel Index (≤55 vs. 60–95 vs. 100), chronic renal failure (absent vs. present), liver cirrhosis (absent vs. present), arrhythmia (absent vs. present), COPD (absent vs. present), chronic lower respiratory tract infection (absent vs. present), CCI (≤2 vs. 3–5 vs. ≥6), BMI (<25 kg/m² vs. 25–30 kg/m² vs. >30 kg/m²), smoking status (never smoker vs. past/current smoker), and distant metastasis (absent vs. present). Potential risk factors with $p < 0.20$ in univariable analyses were adjusted for in multivariable models. In a secondary analysis, the same set of covariates were examined as potential risk factors for ILD among patients receiving gemcitabine plus nab-paclitaxel. Using the logistic regression model with adjustment for potential confounders, we examined risk factors for in-hospital mortality among patients undergoing ILD and calculated odds ratios (ORs) and 95% CIs.

R statistical software (version 4.2.1) and *cmprsk* package (R Development Core Team; http://www.r-project.org) were used to compute cumulative incidence rates and 95% CI at specific time points and conduct Gray's test. All other statistical analyses were performed using Stata statistical software, version 15 (StataCorp LLC, College Station, Texas, USA).

3 | RESULTS

We identified 6163, 9061, 2337, and 227 patients who received gemcitabine plus nab-paclitaxel, gemcitabine monotherapy, gemcitabine plus S-1, and gemcitabine plus erlotinib, respectively, at 205 hospitals (Figure 1). Table 1 summarizes the clinical characteristics of patients with PC according to chemotherapy regimens.

TABLE 1 Baseline characteristics of patients with pancreatic cancer according to chemotherapy regimens.

Characteristic	Chemotherapy regimen				
	Gemcitabine plus nab-paclitaxel (N = 6163)	Gemcitabine monotherapy (N = 9061)	Gemcitabine plus S-1 (N = 2337)	Gemcitabine plus erlotinib (N = 227)	p-value
Age, years	67.4 (9.0)	70.0 (9.4)	65.7 (9.5)	63.7 (8.6)	<0.01
Age ≤74 years	4826 (78%)	5856 (65%)	1918 (82%)	206 (91%)	<0.01
Age ≥75 years	1337 (22%)	3205 (35%)	419 (18%)	21 (9.3%)	
Sex					
Male	3679 (60%)	5071 (56%)	1407 (60%)	130 (57%)	<0.01
Female	2484 (40%)	3990 (44%)	930 (40%)	97 (43%)	
Barthel Index					
100	5795 (94%)	8087 (89%)	2176 (93%)	216 (95%)	<0.01
60–95	285 (4.6%)	709 (7.8%)	115 (4.9%)	9 (4.0%)	
0–55	83 (1.3%)	265 (2.9%)	46 (2.0%)	2 (0.9%)	
Chronic renal failure					
No	6127 (99%)	8947 (99%)	2333 (99%)	227 (100%)	<0.01
Yes	36 (0.6%)	114 (1.3%)	4 (0.2%)	0	
Liver cirrhosis					
No	6111 (99%)	8992 (99%)	2318 (99%)	225 (99%)	0.95
Yes	52 (0.8%)	69 (0.8%)	19 (0.8%)	2 (0.9%)	
Arrhythmia					
No	6138 (99%)	8992 (99%)	2327 (99%)	225 (99%)	0.03
Yes	25 (0.4%)	69 (0.8%)	110 (0.4%)	2 (0.9%)	
COPD					
No	6151 (99%)	9036 (99%)	2335 (99%)	226 (99%)	0.28
Yes	12 (0.2%)	25 (0.3%)	2 (0.1%)	1 (0.4%)	
Chronic lower respiratory tract infection					
No	6077 (98.6%)	8955 (99%)	2309 (99%)	227 (100%)	0.21
Yes	86 (1.4%)	106 (1.2%)	28 (1.2%)	0	
Charlson Comorbidity Index[a]					
≤2	3718 (60%)	5278 (58%)	1418 (61%)	114 (50%)	<0.01
3–5	534 (8.7%)	857 (9.5%)	200 (8.6%)	8 (3.5%)	
≥6	1909 (31%)	2923 (32%)	719 (31%)	105 (46%)	
Body mass index[a]					
<25 kg/m^2	5343 (87%)	7944 (89%)	2058 (89%)	190 (84%)	<0.01
25–30 kg/m^2	687 (11%)	903 (10%)	227 (9.8%)	30 (13%)	
>30 kg/m^2	88 (1.4%)	88 (1.0%)	24 (1.0%)	6 (2.7%)	
Smoking status[a]					
Current or past	2225 (36%)	2784 (34%)	754 (37%)	84 (40%)	<0.01
Never	3281 (64%)	5299 (66%)	1307 (63%)	127 (60%)	
Distant metastasis					
No	2488 (40%)	3275 (36%)	892 (38%)	58 (26%)	<0.01
Yes	3675 (60%)	5786 (64%)	1445 (62%)	169 (74%)	

Note: Data are shown as n (%) or mean (standard deviation).

[a]Patients with missing data were excluded.

Abbreviation: COPD, chronic obstructive pulmonary disease.

ILD was observed in 168 (2.7%) patients receiving gemcitabine plus nab-paclitaxel with a median time to ILD of 2.7 months (interquartile range, 1.8–4.9 months) and in 133 (1.5%) patients receiving gemcitabine monotherapy with a median time to ILD of 2.8 months (interquartile range, 1.8–4.9 months). In patients receiving gemcitabine plus nab-paclitaxel, the cumulative incidence rates of ILD were
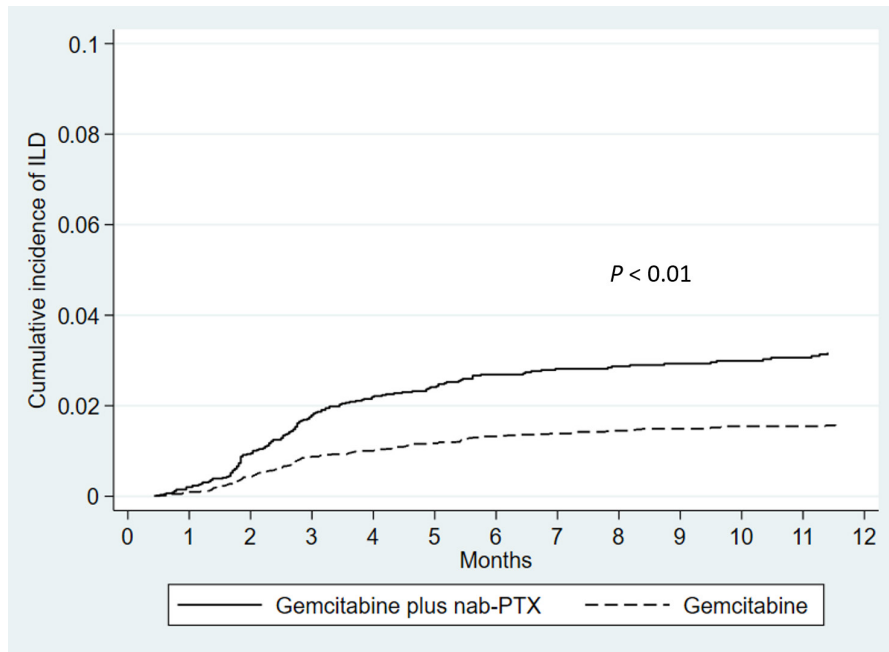
FIGURE 2 Cumulative incidence rates of interstitial lung disease (ILD) among patients with pancreatic cancer by chemotherapy regimens (gemcitabine plus nab-paclitaxel vs. gemcitabine monotherapy). PTX, paclitaxel.

TABLE 2 Characteristics and treatment modalities of patients who developed interstitial lung disease associated with gemcitabine-based chemotherapy.

	Chemotherapy regimen				
	Gemcitabine plus nab-paclitaxel (N = 168)	Gemcitabine monotherapy (N = 133)	Gemcitabine plus S-1 (N = 24)	Gemcitabine plus erlotinib (N = 8)	*p*-value
Demographic					
Age, years	70 (8.0)	72 (8.6)	69 (9.2)	64 (7.3)	0.05
Sex					
Male	109 (65%)	83 (62%)	16 (67%)	8 (100)	0.19
Female	59 (35%)	50 (38%)	8 (33%)	0	
Treatment					
Oxygen therapy	110 (66%)	103 (77%)	17 (71%)	5 (63%)	0.15
Mechanical ventilation	14 (8.3%)	12 (9.0%)	1 (4.2%)	0	0.71
Steroid therapy, any type	137 (82%)	119 (90%)	20 (83%)	6 (75%)	0.24
Oral	29 (17%)	15 (11%)	4 (17%)	0	
Intravenous	24 (14%)	30 (23%)	3 (13%)	1 (13%)	
Both	84 (50%)	74 (56%)	13 (54%)	5 (63%)	<0.01
Intravenous diuretic agent	44 (26%)	52 (39%)	12 (50%)	6 (75%)	

Note: Data are shown as *n* (%) or mean (standard deviation).

2.0% (95% CI: 1.6–2.4), 2.7% (95% CI: 2.2–3.1) and 3.1% (95% CI: 2.6–3.6) at 3, 6, and 12 months, respectively, compared with 0.9% (95% CI: 0.8–1.2), 1.4% (95% CI: 1.1–1.7), and 1.6% (95% CI: 1.3–1.9), respectively, in patients receiving gemcitabine monotherapy (*p* < 0.01, Figure 2). Table 2 summarizes the characteristics of patients who were hospitalized due to ILD and treated during hospitalization. Mechanical ventilation was administered in 14 patients (8.3%) receiving gemcitabine plus nab-paclitaxel and 12 patients (9.0%) receiving gemcitabine monotherapy. In patients receiving gemcitabine plus nab-paclitaxel, most patients received steroid therapy (82%): orally in 29 patients (17%), intravenously in 24 patients (14%), and both in 84 patients (50%). The in-hospital mortality with ILD was 21% and 32% in patients receiving gemcitabine plus nab-paclitaxel and gemcitabine monotherapy, respectively. In the total study population, the incidence of ILD with an in-hospital death was 0.5%. In an analysis of risk factors for in-hospital mortality among patients with ILD, low levels of the Barthel Index and high levels of CCI, but not the chemotherapy regimens, were independent risk factors (Table 3).

TABLE 3 Univariable and multivariable logistic regression analyses to assess the risk factors for in-hospital death among patients with interstitial lung disease.

	N	Events (%)	Univariable			Multivariable[b]		
			Odds ratio	95% CI	p	Odds ratio	95% CI	p
Chemotherapy regimen								
Gemcitabine monotherapy	133	43 (32%)	1	Referent		1	Referent	
Gemcitabine plus nab-paclitaxel	168	36 (21%)	0.57	0.34–0.96	0.03	0.70	0.39–1.24	0.22
Gemcitabine plus S-1	24	9 (38%)	1.25	0.51–3.12	0.62	2.00	0.73–5.53	0.18
Gemcitabine plus erlotinib	8	2 (25%)	0.70	0.14–3.57	0.67	0.56	0.08–3.81	0.56
Age, ≤74 years	219	58 (27%)	1	Referent				
≥75 years	114	32 (28%)	1.08	0.65–1.80	0.78			
Sex, female	117	35 (30%)	1	Referent				
Male	216	55 (26%)	0.80	0.49–1.32	0.38			
Barthel Index, 100	222	47 (21%)	1			1	Referent	
60–95	61	16 (26%)	1.32	0.69–2.55	0.40	1.36	0.68–2.75	0.39
0–55	50	27 (54%)	4.37	2.30–8.31	<0.01	5.27	2.61–10.7	<0.01
Chronic renal failure, No	329	87 (26%)	1	Referent		1	Referent	
Yes	4	3 (75%)	8.34	0.86–81.3	0.07	8.30	0.70–98.9	0.09
Liver cirrhosis, No	329	89 (27%)	1	Referent				
Yes	4	1 (25%)	0.90	0.09–8.75	0.93			
Arrhythmia, No	333	90 (27%)	1	Referent				
Yes	0	0	NA	NA	NA			
COPD, No	328	88 (27%)	1					
Yes	5	2 (40%)	1.82	0.30–11.1	0.52			
Chronic lower respiratory tract infection, No	320	87 (27%)	1					
Yes	13	3 (23%)	0.80	0.22–2.99	0.74			
CCI, ≤2[a]	169	37 (22%)	1	Referent		1	Referent	
3–5	36	9 (25%)	1.19	0.51–2.75	0.69	1.02	0.40–2.63	0.96
≥6	124	43 (35%)	1.89	1.13–3.18	0.02	1.90	1.06–3.39	0.03
BMI <25 kg/m²[a]	303	81 (27%)	1	Referent				
25–30 kg/m²	23	5 (22%)	0.76	0.27–2.12	0.60			
>30 kg/m²	0	0	NA	NA	NA			
Smoking status, Never[a]	163	51 (31%)	1	Referent		1	Referent	
Ever	142	35 (25%)	0.72	0.43–1.19	0.20	0.82	0.47–1.41	0.47
Distant metastasis, No	240	63 (26%)	1	Referent				
Yes	93	27 (29%)	1.15	0.68–1.96	0.61			

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NA, not available.

[a]Patients with missing data were excluded.

[b]The variables with p < 0.20 in the univariable analyses were entered in a multivariable model.

In the multivariable competing-risk regression analysis (Table 4), patients receiving gemcitabine plus nab-paclitaxel were at a higher risk of ILD compared with patients receiving gemcitabine monotherapy or gemcitabine plus S-1 with adjusted SHRs of 1.93 (95% CI: 1.51–2.47) and 2.81 (95% CI: 1.83–4.31), respectively. Erlotinib has been recognized as a risk factor for the development of ILD[8] and, therefore, we compared the risks of ILD between gemcitabine plus nab-paclitaxel and gemcitabine plus erlotinib (Table 4 and Figure S1). No statistically significant difference was observed between the groups although the limited number of patients receiving gemcitabine plus

TABLE 4 Univariable and multivariable competing risks regression analyses to assess the risk of interstitial lung disease associated with gemcitabine plus nab-paclitaxel compared with gemcitabine monotherapy, gemcitabine plus S-1, or gemcitabine plus erlotinib.

Chemotherapy regimen	N	Events (%)	Univariable			Multivariable[a]		
			SHR	95% CI	*p*-value	SHR	95% CI	*p*-value
Gemcitabine monotherapy	9061	133 (1.5%)	1	Referent				
Gemcitabine plus nab-paclitaxel	6163	168 (2.7%)	1.93	1.54–2.42	<0.01	1.93	1.51–2.47	<0.01
Gemcitabine plus S-1	2337	24 (1.0%)	1	Referent				
Gemcitabine plus nab-paclitaxel	6163	168 (2.7%)	2.97	1.94–4.55	<0.01	2.81	1.83–4.31	<0.01
Gemcitabine plus erlotinib	227	8 (3.5%)	1	Referent				
Gemcitabine plus nab-paclitaxel	6163	168 (2.7%)	0.77	0.38–1.55	0.46	0.69	0.34–1.40	0.30

Abbreviations: CI, confidence interval; SHR, subdistribution hazard ratio.

[a]Univariable analysis was conducted by entering each of the following variables: age, sex, Barthel Index, chronic renal failure, liver cirrhosis, arrhythmia, COPD, chronic lung infection, Charlson Comorbidity Index, body mass index, smoking status, and distant metastasis. In addition to the chemotherapy regimen, the variables with *p* < 0.20 in the univariable analyses (age, sex, COPD, Charlson Comorbidity Index, smoking status, and distant metastasis for the comparison with gemcitabine monotherapy; age, sex, and Barthel Index for the comparison with gemcitabine plus S-1; and age and smoking status for the comparison with gemcitabine plus erlotinib) were entered in a multivariable model.

erlotinib precluded a robust statistical assessment in this subgroup. In an analysis of risk factors for ILD in patients receiving gemcitabine plus nab-paclitaxel, older age was an independent risk factor for ILD with an adjusted SHR comparing ≥75 years to ≤74 years of 1.61 (95% CI: 1.16–2.24; Table 5). The adjusted SHR per 10-year increase in age was 1.44 (95% CI: 1.19–1.75). The number of patients with COPD or chronic lower respiratory tract who underwent ILD due to gemcitabine plus nab-paclitaxel was limited, thereby precluding a robust statistical analysis. Among patients receiving gemcitabine monotherapy, smoking status was an independent risk factor for ILD with an adjusted SHR comparing past/current smokers to never smokers of 1.51 (95% CI: 1.00–2.29; Table S1).

4 | DISCUSSION

In this large longitudinal cohort study based on a nationwide database, we characterized the clinical course of patients with PC who developed ILD following gemcitabine plus nab-paclitaxel administration with substantial rates of incidence and in-hospital mortality. Compared with patients receiving gemcitabine monotherapy, patients receiving gemcitabine plus nab-paclitaxel were at a higher risk of ILD, in which older age was the only risk factor. Our population-based data would help to increase the awareness of oncologists on gemcitabine plus nab-paclitaxel-associated ILD and stratify patients who are indicated for this chemotherapy regimen in terms of the ILD risk.

The current study suggests that the addition of nab-paclitaxel may elevate the risk of gemcitabine-associated ILD, which has been well recognized in clinical oncology.[18] Nab-paclitaxel has several potential advantages over conventional solvent-based paclitaxel including increasing the intratumor concentration of paclitaxel and decreasing adverse events (e.g., allergic reactions).[25–28] In the studies of patients with any cancer receiving nab-paclitaxel, the incidence

of ILD was reported to be 6%–8%.[14–16,29,30] Based on our data implicating the additive effects of gemcitabine and nab-paclitaxel on ILD development, clinical oncologists should be aware of this potentially lethal adverse event and pay attention to the early symptoms of ILD (e.g., dyspnea and cough) and chest radiographic changes (typically, interstitial pulmonary infiltrates) when administrating the combination therapy. In this study, the median time to ILD development was approximately 2–3 months after the initiation of gemcitabine with or without nab-paclitaxel; therefore, particular attention should be paid to patients during this period.

Treatment of drug-induced ILD is usually initiated by supportive management including sufficient physical rest and oxygen supplementation. Steroid therapy has been the standard care for patients with moderate to severe ILD, particularly for those with underlying comorbidities and who are unamenable to initial supportive care.[31,32] In the current study, 82% of patients with ILD following gemcitabine plus nab-paclitaxel received intravenous or oral steroid therapy. Given the high in-hospital mortality rate of patients with gemcitabine plus nab-paclitaxel-associated ILD, chemotherapy should be discontinued immediately when symptoms suggestive of ILD development are observed at the clinic, and other chemotherapy regimens should be considered as an alternative subsequent treatment. During hospitalizations associated with ILD, patients should be monitored prudently to avoid delays in administering appropriate intensive treatment options. In addition to that, our analyses suggest that comorbid conditions and physical activity levels may result in fatal outcomes associated with ILD. These findings support the importance of a comprehensive assessment of patients' general conditions in the risk stratification of patients presenting with ILD.[33]

Risk factors for gemcitabine plus nab-paclitaxel-associated ILD have not yet been fully investigated. In prior studies of patients with PC receiving gemcitabine plus nab-paclitaxel, the ABO blood group or concomitant use of Chinese herbal medications

TABLE 5 Univariable and multivariable competing risks regression analyses to assess the risk factors for interstitial lung disease among patients receiving gemcitabine plus nab-paclitaxel.

	N	Events (%)	Univariable			Multivariable[b]		
			SHR	95% CI	p-value	SHR	95% CI	p-value
Age, ≤74 years	4826	118 (2.4%)	1	Referent		1	Referent	
≥75 years	1337	50 (3.7%)	1.58	1.14–2.20	<0.01	1.61	1.16–2.24	<0.01
Sex, female	2484	59 (2.4%)	1	Referent		1	Referent	
Male	3679	109 (3.0%)	1.27	0.92–1.74	0.14	1.30	0.95–1.78	0.11
Barthel Index, 100	5795	159 (2.7%)	1					
60–95	285	5 (1.8%)	0.68	0.28–1.66	0.39			
0–55	83	4 (4.8%)	1.85	0.68–5.01	0.23			
Chronic renal failure, No	6127	168 (2.7%)	1	Referent				
Yes	36	0	NA	NA	NA			
Liver cirrhosis, No	6111	166 (2.7%)	1	Referent				
Yes	52	2 (3.8%)	1.28	0.31–5.20	0.73			
Arrhythmia, No	6138	168 (2.7%)	1	Referent				
Yes	25	0	NA	NA	NA			
COPD, No	6151	168 (2.7%)	1					
Yes	12	0	NA	NA	NA			
Chronic lower respiratory tract infection, No	6077	167 (2.7%)	1					
Yes	86	1 (1.2%)	0.41	0.06–2.99	0.38			
CCI, ≤2[a]	3718	99 (2.7%)	1	Referent				
3–5	534	12 (2.2%)	0.85	0.47–1.53	0.58			
≥6	1909	57 (3.0%)	1.16	0.84–1.61	0.37			
BMI <25 kg/m^{2a}	5343	146 (2.7%)	1	Referent				
25–30 kg/m^2	687	20 (2.9%)	1.08	0.68–1.73	0.73			
>30 kg/m^2	88	2 (2.3%)	0.86	0.21–3.43	0.83			
Smoking status, Never[a]	2225	83 (3.7%)	1	Referent				
Ever	3281	65 (2.0%)	1.19	0.86–1.65	0.29			
Distant metastasis, No	2488	65 (2.6%)	1	Referent				
Yes	3675	103 (2.8%)	1.05	0.77–1.43	0.75			

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; NA, not available; SHR, subdistribution hazard ratio.

[a]Patients with missing data were excluded.

[b]The variables with $p < 0.20$ in the univariable analyses were entered in a multivariable model.

appeared to be associated with the risk of ILD.[14,15] However, those studies were limited by their single-institutional study design and statistical power. The large comprehensive dataset used in this study allowed us to identify risk factors with adjustment for a spectrum of potential confounders. In the current study, a 10-year increase in age translated into an approximately 1.4-fold increased risk of ILD. Older patients might have underlying pulmonary disorders, thereby potentially increasing the risk of drug-induced inflammatory reactions in the lung and resultant ILD.[34,35] Given these findings, the risk of ILD should be recognized, particularly when gemcitabine plus nab-paclitaxel is administered to elderly patients.

This study has several limitations. In our multivariable models, we adjusted for multiple potential confounding factors (e.g., smoking, arrhythmia).[36,37] However, due to the nature of the database used, we could not access some important clinical information, including the results of laboratory tests and imaging studies. Consequently, the ascertainment of ILD cases was based solely on the ICD-10 codes. Nonetheless, those ICD-10 codes were assigned by treating physicians at the participating hospitals. Another limitation was that data at the referred hospital were not available for analysis when a patient was transferred to another hospital. Despite these limitations, a major strength of the current study was the use of large-scale data from many hospitals throughout

Japan, which not only enabled us to document the clinical outcomes of patients with gemcitabine plus nab-paclitaxel-associated ILD with robust statistical estimates, but also potentially ensured the generalizability of our findings.

In conclusion, our large cohort study demonstrated that a substantial incidence rate of ILD was observed in patients with PC who were administered gemcitabine plus nab-paclitaxel. Despite the increased anti-tumor effects of gemcitabine plus nab-paclitaxel for unresectable PC, this combination chemotherapy may increase the risk of ILD compared with gemcitabine monotherapy. Our risk factor analysis suggests that elderly patients who receive gemcitabine plus nab-paclitaxel must be carefully monitored. These findings imply that treatment indications must be assessed considering the trade-off of survival benefits and risk of ILD.

CONFLICT OF INTEREST STATEMENT
None declared.

ETHICS STATEMENT
This study was approved by the institutional review board of The University of Tokyo (Tokyo, Japan; approval number, #3501-(5) [May 19, 2021]).

Informed Consent: The requirement for patients' written informed consent was waived because of the anonymity of the used data.

Registry and the Registration No. of the study: N/A.

Animal Studies: N/A.

ORCID
Tsuyoshi Hamada https://orcid.org/0000-0002-3937-2755
Mitsuhiro Fujishiro https://orcid.org/0000-0002-4074-1140

REFERENCES
1. Ueno H, Ioka T, Ikeda M, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. *J Clin Oncol*. 2013;31:1640-1648.
2. Ueno H, Ikeda M, Ueno M, et al. Phase I/II study of nab-paclitaxel plus gemcitabine for chemotherapy-naive Japanese patients with metastatic pancreatic cancer. *Cancer Chemother Pharmacol*. 2016;77:595-603.
3. Portal A, Pernot S, Tougeron D, et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after Folfirinox failure: an AGEO prospective multicentre cohort. *Br J Cancer*. 2015;113:989-995.
4. Barlési F, Villani P, Doddoli C, Gimenez C, Kleisbauer JP. Gemcitabine-induced severe pulmonary toxicity. *Fundam Clin Pharmacol*. 2004;18:85-91.
5. Belknap SM, Kuzel TM, Yarnold PR, et al. Clinical features and correlates of gemcitabine-associated lung injury: findings from the RADAR project. *Cancer*. 2006;106:2051-2057.
6. Kundranda MN, Niu J. Albumin-bound paclitaxel in solid tumors: clinical development and future directions. *Drug Des Devel Ther*. 2015;9:3767-3777.
7. Nakai Y, Isayama H, Sasaki T, et al. A multicentre randomised phase II trial of gemcitabine alone vs gemcitabine and S-1 combination therapy in advanced pancreatic cancer: GEMSAP study. *Br J Cancer*. 2012;106:1934-1939.
8. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada clinical trials group. *J Clin Oncol*. 2007;25:1960-1966.
9. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369:1691-1703.
10. Goldstein D, El-Maraghi RH, Hammel P, et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. *J Natl Cancer Inst*. 2015;107:dju413.
11. Philip PA, Lacy J, Portales F, et al. Nab-paclitaxel plus gemcitabine in patients with locally advanced pancreatic cancer (LAPACT): a multicentre, open-label phase 2 study. *Lancet Gastroenterol Hepatol*. 2020;5:285-294.
12. Perri G, Prakash L, Qiao W, et al. Response and survival associated with first-line FOLFIRINOX vs gemcitabine and nab-paclitaxel chemotherapy for localized pancreatic ductal adenocarcinoma. *JAMA Surg*. 2020;155:832-839.
13. Viúdez A, Ramírez N, Hernández-García I, Carvalho FL, Vera R, Hidalgo M. Nab-paclitaxel: a flattering facelift. *Crit Rev Oncol*. 2014;92:166-180.
14. Takeda T, Sasaki T, Fukuda K, et al. Risk factors for gemcitabine plus nab-paclitaxel-induced interstitial lung disease in pancreatic cancer patients. *Int J Clin Oncol*. 2021;26:543-551.
15. Ueda R, Yamamoto N, Hori Y, et al. Risk factors for interstitial lung disease induced by gemcitabine plus albumin-bound paclitaxel therapy in pancreatic ductal adenocarcinoma patients. *J Pharm Health Care Sci*. 2022;8:5.
16. Kashiwada T, Saito Y, Terasaki Y, et al. Interstitial lung disease associated with nanoparticle albumin-bound paclitaxel treatment in patients with lung cancer. *Jpn J Clin Oncol*. 2019;49:165-173.
17. Yasuda Y, Nomizo T, Ozasa H, et al. Retrospective analysis of acute exacerbation of interstitial lung diseases with nanoparticle albumin-bound paclitaxel in patients with advanced lung cancer with preexisting interstitial lung disease. *Mol Clin Oncol*. 2017;7:677-680.
18. Hamada T, Yasunaga H, Nakai Y, et al. Interstitial lung disease associated with gemcitabine: a Japanese retrospective cohort study. *Respirology*. 2016;21:338-343.
19. Katsuki R, Jo T, Yasunaga H, Kumazawa R, Uda K. Outcomes of laparoscopic versus open pancreatoduodenectomy: a nationwide retrospective cohort study. *Surgery*. 2021;169:1427-1433.
20. Okada A, Ono S, Yamaguchi S, et al. Association between nutritional guidance or ophthalmological examination and discontinuation of physician visits in patients with newly diagnosed diabetes: a retrospective cohort study using a nationwide database. *J Diabetes Investig*. 2021;12:1619-1631.

21. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Md State Med J*. 1965;14:61-65.

22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-383.

23. Marubini E, Valsecchi MG. *Analysing Survival Data from Clinical Trials and Observational Studies*. John Wiley and Sons; 1995.

24. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496-509.

25. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol*. 2005;23:7794-7803.

26. Shitara K, Takashima A, Fujitani K, et al. Nab-paclitaxel versus solvent-based paclitaxel in patients with previously treated advanced gastric cancer (ABSOLUTE): an open-label, randomised, non-inferiority, phase 3 trial. *Lancet Gastroenterol Hepatol*. 2017;2:277-287.

27. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol*. 2012;30:2055-2062.

28. Stage TB, Bergmann TK, Kroetz DL. Clinical pharmacokinetics of paclitaxel monotherapy: an updated literature review. *Clin Pharmacokinet*. 2018;57:7-19.

29. Miyauchi E, Inoue A, Usui K, et al. Phase II study of modified carboplatin plus weekly nab-paclitaxel in elderly patients with non-small cell lung cancer: North Japan lung cancer study group trial 1301. *Oncologist*. 2017;22:640-e50.

30. Yoshimura N, Sawa K, Nakai T, et al. Phase II study of the modified weekly nab-paclitaxel regimen in previously treated patients with advanced non-small cell lung cancer. *Am J Clin Oncol*. 2021;44:613-618.

31. Podolanczuk AJ, Wong AW, Saito S, Lasky JA, Ryerson CJ, Eickelberg O. Update in interstitial lung disease 2020. *Am J Respir Crit Care Med*. 2021;203:1343-1352.

32. Conte P, Ascierto PA, Patelli G, et al. Drug-induced interstitial lung disease during cancer therapies: expert opinion on diagnosis and treatment. *ESMO Open*. 2022;7:100404.

33. Schwarzkopf L, Witt S, Waelscher J, Polke M, Kreuter M. Associations between comorbidities, their treatment and survival in patients with interstitial lung diseases–a claims data analysis. *Respir Res*. 2018;19(1):73.

34. Margaritopoulos GA, Vasarmidi E, Jacob J, Wells AU, Antoniou KM. Smoking and interstitial lung diseases. *Eur Respir Rev*. 2015;24:428-435.

35. Raghu G, Nyberg F, Morgan G. The epidemiology of interstitial lung disease and its association with lung cancer. *Br J Cancer*. 2004;91(Suppl 2):S3-S10.

36. Bargagli E, Cameli P, Carleo A, et al. The effect of cigarette smoking on bronchoalveolar lavage protein profiles from patients with different interstitial lung diseases. *Panminerva Med*. 2020;62:109-115.

37. Skeoch S, Weatherley N, Swift AJ, et al. Drug-induced interstitial lung disease: a systematic review. *J Clin Med*. 2018;7:356.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.