**ORIGINAL ARTICLE**

# Association between early corticosteroid administration and long-term survival in non-infectious pulmonary complications after allogeneic hematopoietic stem cell transplantation

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## Abstract

Non-infectious pulmonary complications (NIPCs) after allogeneic hematopoietic stem cell transplantation (HSCT) are associated with poor outcomes. It is important to maximize the effectiveness of primary treatment because secondary treatment has not been established. We analyzed data from 393 patients who underwent allogeneic HSCT during a 10-year period. Thirty-seven were diagnosed with NIPCs, which consisted of idiopathic pneumonia syndrome, bronchiolitis obliterans, and interstitial lung disease including cryptogenic organizing pneumonia. Among these, 18 died (Dead group) while 19 remained alive (Alive group) during the study period. The median time between NIPC diagnosis and first administration of $\geq 1$ mg/kg/day corticosteroids (prednisolone dose equivalent) was significantly longer in the Dead group than the Alive group, at 9 days versus 4 days ($p = 0.01$). We further divided these cases into those who received prednisolone within seven days and after 8 days. We found that the $\leq 7$ days group were more likely to survive after their NIPC diagnosis compared to the $\geq 8$ days group ($p = 0.06$). Our analysis showed that early initiation of corticosteroid therapy is associated with long-term survival in NIPCs.

**Keywords** Bronchiolitis obliterans (BO) · Idiopathic pneumonia syndrome (IPS) · Interstitial lung disease (ILD) · Non-infectious pulmonary complications (NIPCs) · Prednisolone

## Introduction

Non-infectious pulmonary complications (NIPCs) after allogeneic hematopoietic cell transplantation (HSCT) are associated with poor outcomes and lower quality of life [1]. NIPCs show various pathological conditions, including idiopathic pneumonia syndrome (IPS), bronchiolitis obliterans (BO), and interstitial lung disease (ILD) including cryptogenic organizing pneumonia (COP). Corticosteroids are widely used for the initial treatment of all these conditions. However, details of the treatment regimen, such as dose and timing, remain unclear.

A diagnosis of NIPCs after HSCT requires excluding infectious diseases as the cause of pneumonia [2], and previous reports also recommend that pneumonia after allogeneic HSCT should be diagnosed based on the patient's immunosuppression profile and potential exposure to infectious risks [3, 4]. Thus, while careful differential diagnosis is required for establishing NIPCs, excluding infections definitively may lead to delay in initiating corticosteroids.

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Ueda et al. determined that the administration of systemic corticosteroids (high-dose methylprednisolone, 1000 mg for 3 days or 0.5–1.0 mg/kg/day prednisolone) for late-onset NIPCs before 21 days from the appearance of respiratory symptoms resulted in significantly better final outcomes compared with the late administration of steroid group [5]. This is the first report showing that early administration of systemic corticosteroids has effective long-term outcomes, however, there have been no reports suggesting the importance of early administration of corticosteroid. Therefore, we aimed to identify an optimal administration timing of corticosteroids that would result in a favorable long-term survival.

## Materials and methods

### Study cohort

This retrospective cohort study analyzed data from patients who underwent allogeneic HSCT at the Okayama University Hospital between 2010 and 2019. For patients who received multiple allogeneic HSCT, only the last allogeneic HSCT performed in each patient during this study period was considered. This study complied with the principles of the Declaration of Helsinki. The institutional review board of the Okayama University Hospital approved the study. Informed consent was obtained in the form of opt-out on the website.

### Transplantation techniques

Myeloablative conditioning regimens were (1) intravenous busulfan (12.8 mg/kg) with cyclophosphamide, (2) cyclophosphamide plus total body irradiation (TBI) (12 Gy) with or without cytarabine, and (3) cyclophosphamide plus TBI (12 Gy) with or without etoposide. Reduced-intensity conditioning regimens included fludarabine with either melphalan (80 mg/kg) or intravenous busulfan (6.4 mg/kg), with or without TBI (2 or 4 Gy). Most patients received a calcineurin inhibitor with short-term methotrexate or mycophenolate mofetil for prophylaxis against graft versus host disease (GVHD). Antimicrobial prophylaxis consisted of levofloxacin during neutropenia, along with acyclovir, trimethoprim-sulfamethoxazole, and fluconazole. Preemptive therapy against cytomegalovirus (CMV) was based on the results of weekly CMV antigenemia assay. The attending physician diagnosed acute or chronic GVHD and graded according to previously described criteria [6, 7].

### Diagnosis of NIPCs

NIPCs were categorized as IPS, BO, or ILD. The diagnoses were based on clinical course, pulmonary function tests, CT images, and pulmonary blood flow scintigraphy reports provided by radiologists and interpreted by pulmonologists. Each NIPCs subclass was defined based on the following characteristics and absence of concurrent infection detected in bronchoalveolar lavage (BAL) or sputum. Specifically, IPS was diagnosed by the presence of at least one of the following: (1) multilobar infiltrates on chest radiograph or computed tomography (CT); (2) symptoms and signs of pneumonia, including dyspnea, cough, cyanosis, hypoxia, or pyrexia; or (3) exacerbation of existing symptoms or appearance of new findings on pulmonary function testing or increased alveolar-arterial oxygen difference [8]. We limited IPS in this study to cases that occurred within 120 days after HSCT [9]. BO was diagnosed based on abnormal results of pulmonary function tests (forced expiratory volume for 1 s [FEV1] < 75% of the predicted value, FEV1/forced vital capacity (FVC) < 0.7) and evidence of air trapping, small airway thickening, or bronchiectasis on high-resolution CT according to the National Institutes of Health criteria [7, 10] when clinical presentation indicative of BO was observed. ILD was diagnosed based on nonspecific respiratory symptoms (fever, dyspnea, and cough), characteristic high-resolution CT that demonstrated patchy and often migratory consolidation in a subpleural, peribronchial, or bandlike pattern, commonly associated with ground-glass opacity and a restrictive ventilatory defect on pulmonary function testing [4, 11]. In this study, ILD included organizing pneumonia and nonspecific interstitial pneumonia. There were no patients with diffuse alveolar damage, acute fibrinous organizing pneumonia, lymphoid interstitial pneumonia, eosinophilic pneumonia, or pleuroparenchymal fibroelastosis [4]. The main endpoint was death or last follow-up after HSCT. We determined the cause of death based on medical records. Observation periods in the Death and Alive groups were calculated from the day of transplantation to death or confirmation of survival, respectively. The observation period of patients who underwent HSCT twice or three times was defined from the last HSCT. The day of NIPCs diagnosis was defined as when imaging findings mentioned above were first detected by chest X-ray or CT scan.

### Corticosteroid dose

Corticosteroids used in NIPCs treatment were converted to prednisolone equivalents such that prednisolone 5 mg,

methylprednisolone 4 mg, and dexamethasone 0.75 mg were deemed equal. Calculations of dose greater than 1 mg per 1 kg of body weight per day (1 mg/kg/day) included steroid pulses with methylprednisolone.

## Statistical analyses

Characteristics of patients with or without NIPCs were compared using the Mann–Whitney $U$ test for continuous variables and Fisher's test for categorical factors. We estimated the cumulative incidence of NIPCs with accounting competing risks. Competing events were considered death without an event. The Fine and Gray proportional hazard model was applied to estimate the subdistribution hazard ratio (SHRs) of NIPCs onset in each factor. Overall survival (OS) of patients with NIPCs was defined as the time from the date of NIPCs diagnosis until death from any causes and censored on the date the patient was last known to be alive. Patients lost to follow-up were censored at the date of last contact/follow-up. The final date of observation was September 9, 2020. We estimated probabilities of OS after diagnosis of NIPCs by the Kaplan–Meier method and compared them using Log-rank test. Cox proportional hazard model was applied to estimate the hazard ratios (HRs) in each factor. In these multivariable analyses, below potential confounders were included; factors with $p < 0.1$ in a univariable analyses and the risk factors for pulmonary complications investigated in previous studies (older age [12], gender [13], smoking history [14], stem cell source (donor from related or peripheral blood stem cell [12], donor-patient gender mismatches especially from female donors to male patients [15]), myeloablative regimen with full-dose TBI [13] and the abnormal result of pulmonary function test before HSCT [12]). All estimates of cumulative incidence, OS, HRs, and SHRs were reported with 95% confidence intervals (CIs). The threshold for significance was $p < 0.05$. All statistical analyses were conducted using EZR version 1.54[16].

## Results

### Study flow chart

Study flow chart is shown in Fig. 1. From January 2010 through December 2019, 458 allogeneic HSCTs were performed in our hospital. The number of patients who underwent allogeneic HSCT twice and three times were 55 and five, respectively; hence, the analysis included data from 393 patients. Among these, 356 patients including 57 with infectious pulmonary complications were free from NIPCs. Thus, 37 patients suffered from NIPCs. Infectious pulmonary complications were caused by bacteria ($n = 34$), fungi (Aspergillus, $n = 25$; Candida, $n = 2$; unknown, $n = 4$), or
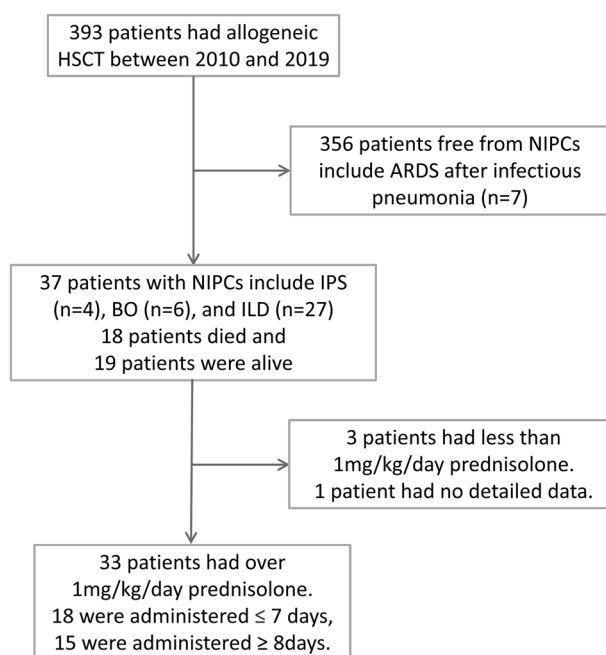


**Fig. 1** Study flow chart. HSCT: hematopoietic stem cell transplantation; NIPCs: non-infectious pulmonary complications; ARDS: acute respiratory distress syndrome; IPS: idiopathic pneumonia syndrome; BO: bronchiolitis obliterans; ILD: interstitial lung disease

CMV ($n = 1$). NIPCs cases included IPS ($n = 4$), BO ($n = 6$), and ILD ($n = 27$). Patients with acute respiratory distress syndrome after infectious pneumonia ($n = 7$) were not categorized as NIPCs. Among NIPCs patients, 18 patients died (Dead group), while 19 patients were alive (Alive group) during a median observation period of 75.1 months (range 2.4–125.5 months) from the date of HSCT to death or last contact/follow-up. Dead group included 14 patients who died of NIPCs exacerbation and 4 patients who died of other causes such as primary disease, gastrointestinal bleeding, severe systemic chronic GVHD, and unknown. Among 37 NIPCs patients, 33 received $\geq 1$ mg/kg/day prednisolone. Three patients were administered less than 1 mg/kg/day prednisolone because of mild and indolent conditions, while detailed data was missing in one case. Of the patients treated with $\geq 1$ mg/ kg/ day prednisolone, 18 received it within 7 days of NIPCs diagnosis, while the prednisolone was administered on day 8 or later in the remaining 15 patients.

### Patient characteristics

The characteristics of all patients ($N = 393$) are shown in Table 1. The median age at transplantation was 53 years [interquartile range (IQR), 42–61], and there were 229 (58.3%) males. There were 129 (32.8%) patients with a history of smoking. There was a gender mismatch of the donor source in 160 (40.7%) patients, half of which were

**Table 1** Characteristics of all patients

|  | All patients ($N = 393$) |
| --- | --- |
| Age at transplantation, median (IQR) | 53 (42–61) |
| Sex (%) | |
| Male | 229 (58.3) |
| Female | 164 (41.7) |
| History of smoking (%) | 129 (32.8) |
| †Smoking index, median (IQR) | 210 (0–400) |
| EOCG PS ≥ 2 (%) | 55 (14.0) |
| Primary disease (%) | |
| AML | 142 (36.1) |
| ALL | 52 (13.2) |
| MDS | 77 (19.6) |
| CML/MPN | 13 (3.3) |
| Lymphoid Malignancy | 64 (16.3) |
| Donor (%) | |
| HLA-matched donor | 201 (51.1) |
| HLA- mismatched donor | 192 (48.9) |
| Stem cell source (%) | |
| UR-BM | 150 (38.2) |
| R-PBSC | 122 (31.0) |
| CB | 86 (21.9) |
| Donor-patient gender (%) | |
| Match | 233 (59.3) |
| Mismatch | 160 (40.7) |
| From female donors to male patients | 80 (20.4) |
| From male donors to female patients | 80 (20.4) |
| Conditioning regimen (%) | |
| MAC | 160 (40.7) |
| RIC | 233 (59.3) |
| Full-dose TBI (12 Gy) (%) | |
| Yes | 90 (22.9) |
| No | 303 (77.1) |
| GVHD prophylaxis (%) | |
| CsA base | 84 (21.4) |
| FK 506 base | 300 (76.3) |
| Pulmonary function test before transplantation | |
| FEV1/ FVC (%), median (IQR) | 81.5 (76.9–115.1) |
| % VC predicted (%), median (IQR) | 100.4 (88.0–112.0) |
| HCT-CI: the risk of pulmonary disorder (%) | |
| ≥ moderate risk | 95 (24.2) |

*IQR* interquartile range, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *AML* acute myeloid leukemia, *ALL* acute lymphocytic leukemia, *MDS* myelodysplastic syndrome, *CML/MPN* chronic myeloid leukemia/myeloproliferative neoplasm, *HLA* human leukocyte antigen, *UR-BM* unrelated bone marrow, *R-PBSC* related peripheral blood stem cell, *CB* cord blood stem cell, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *TBI* total body irradiation, *GVHD* graft vs. host disease, *CsA* cyclosporine A, *FK 506* tacrolimus, *FEV1* forced expiratory volume at 1 s, *FVC* forced vital capacity, *VC* vital capacity, *HCT-CI* hematopoietic cell transplantation-comorbidity index

†The Brinkman index (BI) was used as a measure of cigarette smoke exposure and was calculated as follows: cigarettes per day × smoking years

from female donors to male patients. Regarding preparative regimens, 160 patients (40.7%) received conventional myeloablative conditioning regimens, and 90 patients (22.9%) received full-dose (12 Gy) TBI. The pulmonary function test results before transplantation revealed a median FEV1/FVC of 81.5% (IQR 76.9–115.1) and a median predicted percentage of vital capacity (VC) of 100.4% (IQR 88.0–112.0). Furthermore, 95 (24.2%) patients had a moderate or high risk of pulmonary disorder according to their hematopoietic cell transplantation-comorbidity index (HCT-CI) score.

Characteristics of patients with or without NIPCs are shown in Table 2. The NIPCs group had significantly more men ($p < 0.01$), patients with smoking history ($p = 0.01$), smoking index ≥ 500 ($p < 0.01$) and myelodysplastic syndromes as a primary disease ($p < 0.01$).

## Cumulative incidence of NIPCs

The 5-year cumulative incidence of NIPCs after HSCT was 7.2% (95% CI 4.6–10.4) in this cohort (Fig. 2). Then, donor from related peripheral blood stem cell (SHR 1.67; 95% CI 1.14–2.46; $p < 0.01$) and obstructive ventilatory pattern before HSCT (SHR 1.90; 95% CI 1.07–3.39; $p = 0.03$) were associated with an increased risk for NIPCs onset (Table 3). The male sex, a history of smoking, and a smoking index ≥ 500 tended to be risk factors for NIPCs onset, although these differences were not significant in the multivariable analysis. Other factors investigated by previous reports, such as older age, donor-patient gender mismatches, and myeloablative regimen with full-dose TBI, were not associated with NIPCs onset in our patient cohort.

## Risk factors for death after diagnosis of NIPCs

Most of the patients (36/37; 97.2%) developed the first episode of NIPCs within 36 months after HSCT, but the duration from HSCT to NIPCs diagnosis was not associated with death (dead vs. alive; median days, 175 (IQR 96.8–270.5) vs. median days, 230 (IQR 76.0–370.0); $p = 0.68$) (data not shown). The median time from NIPCs diagnosis to administration of ≥ 1 mg/kg/day prednisolone between the Dead and Alive groups showed significant difference (dead vs. alive; median days, 9 (IQR 7.7–19.0) vs. median days, 4 days (IQR 0.0–7.0) $p = 0.01$) (data not shown). Therefore, we defined the cut-off time as day 7 for further analysis. Administration of 1 mg/kg/day or more prednisolone within 7 days after NIPCs diagnosis was significantly associated with a decreased risk for death (HR 0.20; 95% CI 0.05–0.76; $p = 0.02$) (Table 4). On the other hand, using 1000 mg/body/day as methylprednisolone (HR 8.84; 95% CI 1.32–59.30; $p = 0.02$) and etanercept (HR 62.84; 95% CI 6.93–570.10; $p < 0.01$) as treatment for NIPCs were associated with bad survival (Table 4).

**Table 2** Characteristics of patients with or without NIPCs

| | Free from NIPCs patients (N=356) | NIPCs patients (N=37) | p-value |
|---|---|---|---|
| Age at transplantation ≥ 65 (%) | 43 (12.1) | 8 (21.6) | 0.12 |
| Sex (male) (%) | 197 (55.3) | 32 (86.5) | <0.01* |
| History of smoking (%) | 110 (30.9) | 19 (51.4) | 0.01* |
| †Smoking index ≥ 500 (%) | 49 (13.8) | 14 (37.8) | <0.01* |
| Primary disease (%) | | | |
|   AML | 131 (36.8) | 11 (29.7) | 0.47 |
|   ALL | 51 (14.3) | 1 (2.7) | 0.10 |
|   MDS | 63 (17.7) | 13 (35.1) | <0.01* |
|   CML/MPN | 10 (2.8) | 3 (8.1) | 0.11 |
|   Lymphoid Malignancy | 60 (16.9) | 5 (13.5) | 0.82 |
| HLA mismatch (%) | 178 (50.0) | 15 (40.5) | 0.17 |
| Stem cell source (%) | | | |
|   UR-BM | 131 (36.8) | 19 (51.4) | 0.11 |
|   R-PBSC | 114 (32.0) | 8 (21.6) | 0.26 |
|   CB | 80 (22.5) | 6 (16.2) | 0.53 |
|   Others | 31 (8.7) | 4 (10.8) | |
| Donor-patient gender mismatches (%) | 149 (41.9) | 11 (29.7) | 0.16 |
|   From female donors to male patients (%) | 69 (19.4) | 11 (29.7) | 0.20 |
| Conditioning regimen (%) | | | |
|   MAC | 147 (41.3) | 14 (37.8) | 0.42 |
|   Full-dose TBI (12 Gy) | 81 (22.8) | 9 (24.3) | 0.87 |
| GVHD prophylaxis (%) | | | |
|   CsA base | 76 (21.3) | 7 (18.9) | 1.00 |
|   FK 506 base | 272 (76.4) | 30 (81.1) | 1.00 |
| Pulmonary function test before transplantation (%) | | | |
|   FEV1/ FVC < 70% | 19 (5.3) | 5 (13.5) | 0.06 |
|   % VC predicted < 80% | 37 (10.4) | 3 (8.1) | 0.54 |
|   FEV1.0/ FVC < 70% + % VC predicted < 80% | 9 (2.5) | 0 (0.0) | 1.00 |
| HCT-CI: the risk of pulmonary disorder | | | |
|   ≥ moderate risk (%) | 83 (23.3) | 12 (32.4) | 0.23 |

Statistical differences between the free from NIPCs group and the NIPCs group in the factors shown in this Table were evaluated using Fisher's test. They are represented as *p*-values. *$p < 0.05$ was considered statistically significant

*NIPCs* non-infectious pulmonary complications, *AML* acute myeloid leukemia, *ALL* acute lymphocytic leukemia, *MDS* myelodysplastic syndrome, *CML/MPN* chronic myeloid leukemia/myeloproliferative neoplasm, *HLA* human leukocyte antigen, *UR-BM* unrelated bone marrow, *R-PBSC* related peripheral blood stem cell, *CB* cord blood stem cell, *MAC* myeloablative conditioning, *TBI* total body irradiation, *GVHD* graft vs. host disease, *CsA* cyclosporine A, *FK 506* tacrolimus, *FEV1* forced expiratory volume at 1 s, *FVC* forced vital capacity, *VC* vital capacity, *HCT-CI* hematopoietic cell transplantation-comorbidity index

†The Brinkman index (BI) was used as a measure of cigarette smoke exposure and was calculated as follows: cigarettes per day × smoking years

Next, 16 out of 37 NIPCs patients underwent bronchoscopy to exclude infection. There was no difference of the timing of bronchoscopy between Dead and Alive group [median days 6.5 (IQR 2.8–14.0) vs. median days, 6.0 (IQR 4.0–9.8); $p = 0.86$] (data not shown).

## Relationship between the timing of steroid administration and survival based on NIPCs subtypes

We divided Dead and Alive NIPCs patients ($n = 33$) into those provided ≥ 1 mg/kg/day prednisolone within 7 days after NIPCs diagnosis ($n = 18$) and those who were administered the drug on day eight or later ($n = 15$). Patients administered corticosteroid before day 7 tended to show
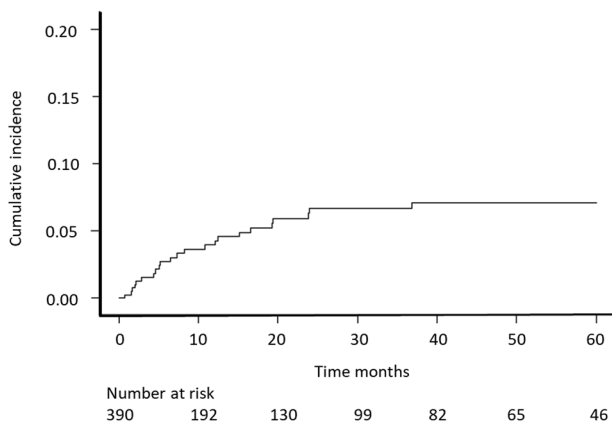
**Fig. 2** Cumulative incidence rate of NIPCs at 60 months after HSCT with accounting competing risks was 7.2% (95% CI 4.6–10.4)

better survival than those provided the drug after day 8; specifically, 3-year OS in the within seven days vs. over eight days groups were 72.2% (95% CI 45.6%–87.4%) and 45.7% (95% CI 20.1%–68.3%), respectively (*p* = 0.06) (Fig. 3A). Moreover, the relationship between the timing of steroid administration and survival was evaluated based on NIPCs subtypes. Although there was no significant difference, the survival among ILD patients tended to be better in the group administered steroids within seven days (*p* = 0.06) (Fig. 3D).

### Reasons for delayed administration of ≥ 1 mg/kg/day prednisolone

Among 15 patients who were administered corticosteroids 8 days or later after NIPCs diagnosis, 11 were initially treated assuming infectious pneumonia because excluding it before starting corticosteroids was prioritized in these patients (Table 5). Only four patients (No. 3, No. 5, No. 11 and No. 14) had a concomitant infection. In the case of patient No. 5, infectious pneumonia was suspected because *Pseudomonas aeruginosa* was detected upon sputum culture. However, antibiotic therapy against *P. aeruginosa* was unsuccessful, and corticosteroids were initiated after establishing lymphocyte predominance and disappearance of *P. aeruginosa* in BAL. Patient No. 14 was treated as CMV pneumonia initially because of CMV antigenemia before starting administration of corticosteroids for NIPCs. In the case of No. 3, No. 11, the reason for hesitating to initiate ≥ 1 mg/kg/day prednisolone was the presence of opportunistic infection and primary refractory disease. Additionally, No. 10 and No. 13 had abnormal findings on chest CT but were not treated for NIPCs because the attending physicians had determined that there was no urgent need to administer corticosteroids.

In contrast, the main reasons for early administration of corticosteroids were GVHD combined with NIPCs, severe symptoms, and typical NIPCs findings on CT (data not shown). These patients were treated with ≥ 1 mg/kg/day prednisolone combined with broad-spectrum antibiotics from the early phase.

## Discussion

Our study shows that administration of ≥ 1 mg/kg/day prednisolone within seven days after NIPCs diagnosis was associated with long-term survival. The median time from NIPCs diagnosis to administration of corticosteroids was significantly lower in the Alive group than in the Dead group, and early administration of corticosteroids tended to result in better long-term survival (*p* = 0.06). This report identifies the timing of corticosteroid administration as a factor that contributes to long-term survival in NIPCs.

NIPCs include various subtypes such as IPS, BO, and ILD. Reported incidence rates of IPS after allogeneic HSCT was from 7 to 35%, and associated mortality rates are as high as 75% [17]. Although initial treatment is corticosteroid therapy, it is not sufficiently effective, and no second-line regimens have been established. Further, while a combination of corticosteroids and TNFα inhibitors has been reported to be effective against IPS in a preclinical model, the results of clinical randomized controlled trials were negative [18]. The first-line therapy for BO is also corticosteroids. It is based on its association with acute or chronic GVHD in the lung; however, no treatment improves long-term survival of patients with corticosteroids resistance. Nevertheless, a combination of fluticasone, azithromycin, and montelukast was evaluated in a prospective, open-label, non-randomized trial. This combination has often been used in clinical trials practice because it results in FEV1 stabilization and a reduction in corticosteroid requirement [19]. ILD can develop during the late period after HSCT, and it is reportedly associated with chronic GVHD, especially in COP [15, 20]. ILD accounts for 12–60% of all late-onset NIPCs, and its median time-to onset after HSCT is 11.3 months [4]. ILD is characterized by a mixture of ground-glass opacities and infiltration shadows on CT. The main pulmonary function pattern is a restrictive ventilatory defect and the median survival at 24 months was 61% [21].

Even though corticosteroids are widely used for the initial treatment of NIPCs, regardless of the type of disease, no promising second-line therapy has been reported. Therefore, it is important to maximize the effects of corticosteroids as an initial treatment. Ueda et al. reported that early (before 21 days from the onset of respiratory symptoms) systemic corticosteroid administration (high-dose methylprednisolone, 1000 mg for 3 days or 0.5–1.0 mg/kg/day prednisolone) was significantly associated with a better final outcome of late-onset NIPCs, while a late (after 22 days from

**Table 3** Univariable and multivariable analyses for cumulative incidence of NIPCs

| | Number of others/NIPCs | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|---|
| | | SHR (95% CI) | *p*-value | SHR (95% CI) | *p*-value |
| Age at transplantation ≥ 65 | 43/8 | 1.43 (0.61–3.32) | 0.41 | 1.09 (0.52–2.25) | 0.82 |
| Sex (male) | 197/32 | 3.58 (1.27–10.08) | 0.02* | 0.97 (0.61–1.54) | 0.89 |
| History of smoking | 110/19 | 1.45 (1.05–2.00) | 0.03* | 0.83 (0.25–2.80) | 0.77 |
| †Smoking index ≥ 500 | 49/14 | 3.16 (1.57–6.37) | < 0.01* | 1.65 (0.52–5.28) | 0.40 |
| Primary disease | | | | | |
| AML | 131/11 | 0.62 (0.19–2.09) | 0.44 | | |
| ALL | 51/1 | 0.23 (0.03–2.03) | 0.18 | | |
| MDS | 63/13 | 1.13 (0.31–4.07) | 0.85 | | |
| CML/MPN | 10/3 | 3.12 (0.69–14.19) | 0.14 | | |
| Lymphoid malignancy | 60/5 | 1.00 (0.27–3.72) | 1.00 | | |
| Others | 41/4 | | | | |
| HLA mismatch | 178/15 | 1.76 (0.66–4.64) | 0.26 | | |
| Stem cell source | | | | | |
| UR–BM | 131/19 | 0.96 (0.28–3.36) | 0.95 | | |
| R–PBSC | 114/8 | 0.66 (0.12–3.68) | 0.63 | 1.67 (1.14–2.46) | < 0.01* |
| CB | 80/6 | 0.68 (0.09–5.50) | 0.72 | | |
| Others | 31/4 | | | | |
| Donor-patient gender mismatches | 149/11 | 0.69 (0.33–1.44) | 0.32 | | |
| From female donors to male patients | 69/11 | 1.65 (0.81—3.36) | 0.17 | 0.88 (0.31–2.47) | 0.81 |
| Conditioning regimen | | | | | |
| MAC | 147/14 | 0.99 (0.44–2.23) | 0.98 | | |
| Full-dose TBI (12 Gy) | 81/9 | 2.63 (0.79–8.73) | 0.11 | 0.86 (0.69–1.06) | 0.15 |
| GVHD prophylaxis | | | | | |
| CsA base | 76/7 | 0.42 (0.03–5.43) | 0.50 | | |
| FK 506 base | 272/30 | 0.39 (0.05–3.28) | 0.38 | | |
| Pulmonary function test before transplantation | | | | | |
| FEV1/ FVC < 70% | 19/5 | 1.83 (1.12–2.99) | 0.02* | 1.90 (1.07–3.39) | 0.03* |
| % VC predicted < 80% | 37/3 | 0.94 (0.51–1.70) | 0.83 | | |
| FEV1.0/ FVC < 70% + % VC predicted < 80% | 9/0 | 0.45 (0.06–3.22) | 0.43 | | |
| HCT-CI: the risk of pulmonary disorder | | | | | |
| ≥ moderate risk | 83/12 | 1.44 (0.71–2.93) | 0.31 | | |

Cumulative incidence of NIPCs was evaluated using Fine and Gray method in univariable and multivariable analyses. Statistical differences between the free from NIPCs group and the NIPCs group in the factors shown in this Table are represented as *p*-values. *$p < 0.05$ was considered statistically significant

*NIPCs* non-infectious pulmonary complications *SHR* subdistribution hazard ratio, *CI* confidence intervals, *AML* acute myeloid leukemia, *ALL* acute lymphocytic leukemia, *MDS* myelodysplastic syndrome, *CML/MPN* chronic myeloid leukemia/myeloproliferative neoplasm, *HLA* human leukocyte antigen, *UR-BM* unrelated bone marrow, *R-PBSC* related peripheral blood stem cell, *CB* cord blood stem cell, *MAC* myeloablative conditioning, *TBI* total body irradiation, *GVHD* graft vs. host disease, *CsA* cyclosporine A, *FK 506* tacrolimus, *FEV1*: forced expiratory volume at 1 s, *FVC* forced vital capacity, *VC* vital capacity, *HCT-CI* hematopoietic cell transplantation-comorbidity index

†The Brinkman index (BI) was used as a measure of cigarette smoke exposure and was calculated as follows: cigarettes per day × smoking years

onset) dose of systemic corticosteroids failed to influence the final outcome [5]. Likewise, in our cohort, the survival in the early administration group was better, though the early administration group had more patients with severe condition: the requirement of 10 L supplemental oxygen with simple mask or special management in the intensive care unit at NIPCs onset ($p = 0.048$, data not shown). These results may indicate that early administration of corticosteroids prevents pulmonary fibrosis caused by immune reactions after HSCT and leads to better outcomes. Previous reports demonstrated that delayed administration of corticosteroids increased relapse of COP [22] and early administration of dexamethasone leads to a good outcome in preterm infants by inhibiting fibrogenic mediators [23]. Moreover, in our study, patients who received ≥ 1 mg/kg/day prednisolone within 7 days after NIPCs diagnosis also showed faster

**Table 4** Univariable and multivariable analyses for survival among patients with NIPCs

| | Number of dead (N=18)/alive (N=19) | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|---|
| | | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Age at transplantation ≥ 65 | 1/7 | 0.21 (0.03–1.55) | 0.13 | | |
| Sex (male) | 16/16 | 1.72 (0.39–7.58) | 0.47 | | |
| History of smoking | 8/11 | 0.82 (0.27–2.51) | 0.73 | | |
| †Smoking index ≥ 500 | 6/8 | 0.77 (0.26–2.30) | 0.64 | | |
| Status of primary disease at transplantation (non-remission) | 9/11 | 1.07 (0.42–2.73) | 0.88 | | |
| HLA mismatch | 8/7 | 1.10 (0.43–2.80) | 0.84 | | |
| Stem cell source | | | | | |
|   UR-BM | 10/9 | 1.12 (0.44–2.83) | 0.82 | | |
|   R-PBSC | 4/4 | 1.13 (0.37–3.43) | 0.83 | | |
|   CB | 2/4 | 0.62 (0.14–2.69) | 0.52 | | |
|   Others | 2/2 | | | | |
| Conditioning regimen MAC | 7/7 | 0.93 (0.36–2.42) | 0.89 | | |
| GVHD prophylaxis | | – | | | |
|   CsA base | 3/4 | 1.05 (0.35–3.20) | 0.93 | | |
|   FK 506 base | 15/15 | 1.31 (0.38–4.54) | 0.67 | | |
| Pulmonary function test before transplantation | | | | | |
|   FEV1/ FVC < 70% | 1/4 | 0.27 (0.04–2.05) | 0.21 | | |
|   % VC predicted < 80% | 0/3 | 1.26 (0.29–5.50) | 0.76 | | |
| HCT-CI ≥ 3 | 4/5 | 0.97 (0.32–2.99) | 0.96 | | |
| Pulmonary complication at transplantation | 6/7 | 0.90 (0.34–2.43) | 0.84 | | |
| ECOG PS 2–4 at transplantation | 1/3 | 0.51 (0.07–3.82) | 0.51 | | |
| ECOG PS 2–4 at NIPCs diagnosis | 8/6 | 2.15 (0.84–5.46) | 0.11 | | |
| NIPCs | | – | | | |
|   IPS | 2/2 | 1.08 (0.24–4.79) | 0.92 | | |
|   BO | 2/4 | 0.45 (0.10–1.99) | 0.29 | | |
|   ILD | 14/13 | 1.66 (0.54–5.14) | 0.38 | | |
| a/c GVHD history before NIPCs diagnosis | 8/8 | 1.15 (0.45–2.93) | 0.77 | | |
| Symptoms at the onset | | – | | | |
|   Respiratory symptoms | 14/15 | 1.12 (0.37–3.41) | 0.84 | | |
|   Fever | 8/8 | 1.08 (0.42–2.73) | 0.88 | | |
|   Need oxygen administration | 12/11 | 1.48 (0.52–4.20) | 0.47 | | |
| Treatment | | – | | | |
|   Corticosteroids | 18/19 | NA (NA–NA) | NA | | |
|   1 mg/kg/day or more as prednisolone | 16/17 | 1.10 (0.25–4.80) | 0.90 | | |
|   1000 mg/body/day as methylprednisolone | 3/1 | 5.70 (1.56–20.88) | <0.01* | 8.84 (1.32–59.30) | 0.02* |
|   1 mg/kg/day or more prednisolone within 7 days after NIPCs diagnosis | 5/13 | 0.39 (0.14–1.12) | 0.08 | 0.20 (0.05–0.76) | 0.02* |
|   Combined with ††inhaled drug | 3/2 | 1.48 (0.42–5.19) | 0.54 | | |
|   Etanercept††† | 4/0 | 27.37 (4.80–156.00) | <0.01* | 62.84 (6.93–570.10) | <0.01* |
|   Ventilator (endotracheal intubation, nasal high-flow) | 8/2 | 4.88 (1.83–13.01) | <0.01* | 2.23 (0.56–8.90) | 0.26 |
|   Home oxygen therapy | 1/1 | 0.58 (0.08–4.45) | 0.60 | | |

Relationships between factors and survival from the diagnosis of NIPCs until the date of death or last follow-up were evaluated using Cox proportional hazards regression in univariable and multivariable analyses. Statistical differences between the dead and alive groups in the factors shown in this Table are represented as p-values. *$p < 0.05$ was considered statistically significant

*NIPCs* non-infectious pulmonary complications, *HR* hazard ratio, *CI* confidence intervals, *HLA* human leukocyte antigen; *UR-BM* unrelated bone marrow, *R-PBSC* related peripheral blood stem cell, *CB* cord blood stem cell, *MAC* myeloablative conditioning, *GVHD* graft vs. host disease, *CsA* cyclosporine A, *FK 506* tacrolimus, *FEV1* forced expiratory volume at 1 s, *FVC* forced vital capacity, *VC* vital capacity, *HCT-CI* hematopoietic cell transplantation-comorbidity index, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *IPS* idiopathic pneumonia syndrome, *BO* bronchiolitis obliterans, *ILD* interstitial lung disease, *a/c* acute or chronic

†The Brinkman index (BI) was used as a measure of cigarette smoke exposure and was calculated as follows: cigarettes per day × smoking years

††Inhaled corticosteroid or treatment with fluticasone, azithromycin, and montelukast
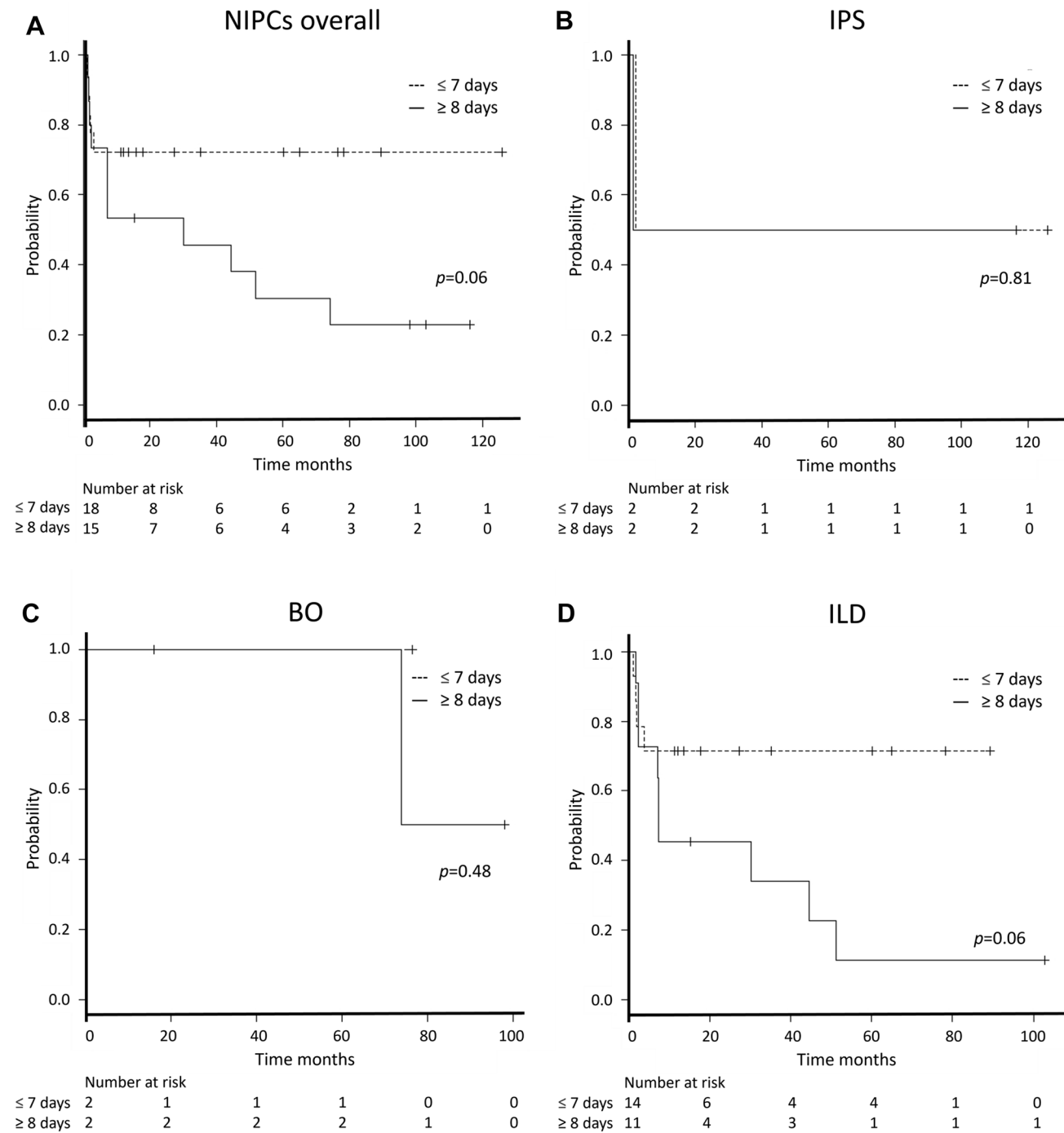
†††A tumor necrosis factor inhibitor

**Fig. 3** Relationship between the timing of steroid administration and survival based on NIPCs subtypes. Survival probabilities between steroid administration ≤7 days and ≥8 days groups in each NIPCs subtype, **A** NIPCs overall, **B** IPS, **C** BO, **D** ILD, were estimated using Log-rank test. We defined $p < 0.05$ as statistically significant. Abbre-

viations; NIPCs: non-infectious pulmonary complications; IPS: idiopathic pneumonia syndrome; BO: bronchiolitis obliterans; ILD: interstitial lung disease; ≤7 days: administration of corticosteroids within 7 days from NIPCs diagnosis; >8 days: administration of corticosteroids after 8 days from NIPCs diagnosis

tapering, i.e., 25% or greater reduction of corticosteroid dose within 1 month was shown in 10 of 18 patients in the early group but only in 3 of 15 cases in late group ($p = 0.03$, data not shown). This may contribute to improving survival after

NIPCs onset due to preventing infections or other complications caused by long-term administration of corticosteroids.

Various reports have stated that excluding infectious diseases was essential for the diagnosis of NIPCs [2], and

**Table 5** The reasons of delayed administration of over 1 mg/kg/day as prednisolone

| Patient no. | Disease | NIPCs—corticosteroids[a] | HSCT—NIPCs[b] | NIPCs—last follow-up[c] | Death | Combined with a/c GVHD[d] | Combined with infection[e] | Reason |
|---|---|---|---|---|---|---|---|---|
| 1 | BO | 8 | 187 | 217 | Yes | Yes | – | Treated as bacterial pneumonia |
| 2 | ILD | 8 | 290 | 920 | Yes | – | – | Treated as bacterial pneumonia |
| 3 | BO | 9 | 157 | 221 | Yes | – | Yes | Combined with CMV antigenemia and primary disease refractory |
| 4 | ILD | 11 | 197 | 466 | – | – | – | Treated as PCP |
| 5 | IPS | 14 | 31 | 42 | Yes | – | Yes | Treated as infectious pneumonia because of shortly after engraftment and detection of Pseudomonas aeruginosa in sputum culture |
| 6 | ILD | 16 | 263 | 74 | Yes | – | – | Treated as infectious pneumonia until excluding infections |
| 7 | ILD | 20 | 249 | 3131 | – | Yes | – | Treated as bacterial pneumonia |
| 8 | IPS | 22 | 22 | 3548 | – | – | – | Treated as bacterial pneumonia |
| 9 | ILD | 28 | 382 | 223 | Yes | Yes | – | Treated as PCP until excluding infections |
| 10 | BO | 33 | 139 | 2987 | – | Yes | – | No treatment follow-up because of mild symptoms |
| 11 | ILD | 35 | 118 | 53 | Yes | Yes | Yes | Combined with hemorrhagic cystitis and primary disease refractory |
| 12 | BO | 40 | 586 | 2250 | Yes | Yes | - | Treated as bacterial pneumonia |
| 13 | ILD | 834 | 728 | 1557 | Yes | – | – | No treatment follow-up because of mild symptoms. Even though after NIPCs exacerbation, the doctor did not increase the amount of steroids because the patient concerned about side effects |
| 14 | ILD | 31 | 86 | 1355 | Yes | – | Yes | Combined with CMV antigenemia and treated as CMV pneumonia |
| 15 | ILD | 15 | 247 | 69 | Yes | Yes | – | Treated as fungal pneumonia |

*NIPCs* non-infectious pulmonary complications, *HSCT* hematopoietic stem cell transplantation, *GVHD* graft vs host disease, *BO* bronchiolitis obliterans, *ILD* interstitial lung disease, *CMV* cytomegalovirus, *PCP* pneumocystis pneumonia, *IPS* idiopathic pneumonia syndrome

[a]Days after NIPCs diagnosis to administration of 1 mg/kg/day or more as prednisolone

[b]Days after HSCT to NIPCs diagnosis

[c]Days after NIPCs diagnosis to last follow-up

[d]Combined with acute or chronic GVHD at the time of NIPCs diagnosis

[e]Combined with infection at the time of NIPCs diagnosis

this requirement has a considerable influence on the timing of corticosteroid initiation. There were many cases in our cohort wherein corticosteroid administration was delayed due to concerns about infectious pneumonia, when in fact, bronchoscopy results in most patients, such as greater lymphocytes than neutrophils, were suggestive of NIPCs rather than infectious pneumonia. Congruently, there was only one case of concurrent NIPCs and infectious pneumonia in our cohort. Infections pneumonia after HSCT, such as bacterial pneumonia, invasive aspergillosis, pneumocystis pneumonia, and respiratory virus infection, may also be associated with lung dysfunction and non-infectious pulmonary complications as BO and IPS [24–26]. However, the occurrence of bacterial pneumonia at 100 days after HSCT is uncommon [3], and the incidence of pneumocystis pneumonia in patients who strictly adhere to the sulfamethoxazole-trimethoprim regimen is extremely low [27]. In contrast, patients with GVHD are likely to develop infectious pneumonia because they are immunosuppressed. Therefore, it is necessary to evaluate the risk of infection based on the patient's immunosuppressive status [3].

Noninvasive diagnostic methods such as nasopharyngeal respiratory virus panel-polymerase chain reaction (PCR), galactomannan antigen, and CMV PCR are useful tools for early diagnosis of infectious, non-infectious, or mixed conditions in patients with post-HSCT pneumonia [28]. Previous reports show that nasopharyngeal respiratory virus PCR testing is highly concordant with BAL testing [29], and hence, they should be actively used for diagnosis. Furthermore, as

prevention of infectious pneumonia is critical, all patients should be prescribed sulfamethoxazole-trimethoprim, acyclovir, and antifungal drugs, as appropriate, after HSCT. Patients should be tested regularly for CMV antigen, with vaccination against *Streptococcus pneumoniae* and *Hemophilus influenzae* recommended at an appropriate time, irrespective of whether these prophylactic measures are important for differentiating between infectious or non-infectious conditions during diagnosis. Given the limited treatment options for NIPCs, patients should be monitored carefully after HSCT through regular outpatient visits, review of the patient's respiratory symptoms, and suitability of treatment regimen [30].

Our study has some limitations. First, this was a retrospective analysis of a cohort drawn from a single institute consisting of a relatively small number of patients. This precluded a reliable evaluation of the risk factors for each NIPCs subtype. Additionally, although we included available potential confounders in the multivariable analyses, we could not identify risk factors for NIPCs reported in previous studies [13, 31, 32]. Other factors might have led to biased results. Second, we did not directly analyze the causal relationship between early steroid administration to patients with NIPCs and survival, but there was a significant difference in the correlation. The results might also have been influenced by a potential selection bias in the timing of corticosteroid administration and by other confounding factors. Third, we did not completely rule out pneumonia caused by respiratory viruses, such as human rhinovirus, since there is no commercially available method for screening respiratory viruses in Japan.

In conclusion, we focused on the optimal time and dose of corticosteroid therapy in patients with NIPCs and showed that steroid administration within seven days of NIPCs diagnosis was associated with long-term survival. Although the exclusion of infectious diseases is important for the diagnosis of NIPCs, our results show that, due to the development of biological testing and infection prevention in recent years, it is possible to initiate corticosteroids early for NIPCs, along with broad-spectrum antibiotics. Further studies and additional data are needed to verify the results presented here.

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## Conflict of interest

The authors declare that they have no conflict of interest.

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