Acute and Critical Care

Acute and Critical Care 2022 Novemebr 37(4):561-570
https://doi.org/10.4266/acc.2022.00444

| pISSN 2586-6052 | eISSN 2586-6060

Association between timing of intubation and mortality in patients with idiopathic pulmonary fibrosis

Eunhye Bae[1], Jimyung Park[1], Sun Mi Choi[1], Jinwoo Lee[1], Sang-Min Lee[1,2], Hong Yeul Lee[2]

[1]*Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine and* [2]*Department of Critical Care Medicine, Seoul National University Hospital, Seoul, Korea*

Background: Delayed intubation is associated with poor prognosis in patients with respiratory failure. However, the effect of delayed intubation in patients with idiopathic pulmonary fibrosis (IPF) remains unknown. This study aimed to analyze whether timing of intubation after high-concentration oxygen therapy was associated with worse clinical outcomes in IPF patients.

Methods: This retrospective propensity score-matched study enrolled adult patients with IPF who underwent mechanical ventilation between January 2011 and July 2021. Patients were divided into early and delayed intubation groups. Delayed intubation was defined as use of high-concentration oxygen therapy for at least 48 hours before tracheal intubation. The primary outcome was intensive care unit (ICU) mortality, and a conditional logistic regression model was used to evaluate the association between timing of intubation and clinical outcomes.

Results: The median duration of high-concentration oxygen therapy before intubation was 0.5 days in the early intubation group (n=60) and 5.1 days in the delayed intubation group (n=36). The ICU mortality rate was 56.7% and 75% in the early and delayed intubation groups, respectively, before propensity matching (P=0.075). After matching for demographic and clinical covariates, 33 matched pairs were selected. In the propensity-matched cohort, delayed intubation significantly increased the risk of ICU mortality (adjusted odds ratio, 3.99; 95% confidence interval, 1.02–15.63; P=0.046). However, in-hospital mortality did not differ significantly between the groups.

Conclusions: In patients with IPF, delayed intubation after initiation of high-concentration oxygen therapy was significantly associated with increased risk of ICU mortality compared to early intubation.

Key Words: idiopathic pulmonary fibrosis; intubation; mortality

Original Article

Received: April 4, 2022
Revised: July 4, 2022
Accepted: July 18, 2022

Corresponding author
Hong Yeul Lee
Department of Critical Care Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-2957
Fax: +82-2-762-9662
E-mail: takumama@naver.com

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and fibrosing interstitial pneumonia of unknown cause. The prevalence of IPF was 2–29 cases per 100,000 in the general population [1]. IPF has a poor prognosis and limited treatment options. According to the American Thoracic Society (ATS) guidelines, antifibrotic drugs such as pirfenidone and nintedanib are recommended to treat IPF; corticosteroids may be helpful during acute exacerbation of IPF [1,2]. Lung transplantation (TPL) is strongly recommended for patients having IPF

with a progressively incurable nature.

Mechanical ventilation is not recommended due to the high mortality associated with mechanical ventilation in patients with IPF (approximately 80–90%) [3,4]. In a minority of cases, however, mechanical ventilation is reasonable [1]. In some patients with IPF, invasive mechanical ventilation can be implemented as a bridge to lung TPL [5,6]. Recently, with the development of critical medical care, the rate of mechanical ventilation in patients with IPF has gradually increased. According to a previous study, the number of patients with IPF with respiratory failure that required mechanical ventilation increased by 61% from 5.9 per 100,000 hospitalizations in 2013 to 9.5 per 100,000 hospitalizations in 2017 [7]. Although the use of mechanical ventilation is increasing in IPF patients, there are no precise guidelines for optimizing both patient selection and timing of intubation in IPF patients with respiratory failure.

With the development of oxygen therapy for improving patient oxygenation, high-flow oxygen therapy, such as through the use of a high-flow nasal cannula (HFNC), could reduce the need for tracheal intubation [8]. However, use of HFNC in patients with respiratory failure may delay intubation and worsen the clinical outcomes [9]. Delayed intubation showed a poor prognosis in a study of patients with acute respiratory distress syndrome (ARDS) [10]. However, these studies analyzed patients with respiratory failure, including those with several etiologies. The association between timing of tracheal intubation and clinical prognosis may differ depending on the cause of respiratory failure. Furthermore, few studies on the effect of intubation timing on clinical outcomes in patients with IPF have been attempted. Therefore, this study aimed to analyze the association between timing of intubation and clinical outcomes in patients with IPF who require invasive mechanical ventilation after starting high-concentration oxygen therapy.

KEY MESSAGES

- Although delayed intubation is associated with poor prognosis in patients with respiratory failure, the effect of delayed intubation in patients with idiopathic pulmonary fibrosis (IPF) remains unknown.
- Delayed intubation, defined as use of high-concentration oxygen therapy for at least 48 hours before tracheal intubation, was significantly associated with increased risk of intensive care unit mortality compared to early intubation in patients with IPF that required mechanical ventilation.
- As with other causes of respiratory failure, tracheal intubation should not be delayed if needed in IPF patients who have failed high-concentration oxygen therapy, especially when lung transplantation is being considered.

MATERIALS AND METHODS

Study Design and Population

Our retrospective observational study included adult patients (>19 years) diagnosed with IPF who were admitted to the intensive care unit (ICU) and received mechanical ventilation from January 2011 to July 2021. Patients diagnosed with IPF according to the ATS guidelines [11] and who received high-concentration oxygen therapy before intubation were enrolled and followed up until hospital discharge or death. Patients aged <19 years, admitted to the ICU but not undergoing intubation, admitted to the ICU for surgery such as lung TPL, transferred after oxygen therapy or tracheal intubation at another hospital, and who underwent tracheal intubation upon arrival at the hospital were excluded from the study. The Institutional Review Board of Seoul National University Hospital waived the requirement for written informed consent due to the retrospective nature of the study and approved this study (No. IRB-H-2106-185-1230).

Definitions and Data Collection

High-concentration oxygen therapy was defined as delivery of a greater than 40% fraction of inspired oxygen (FiO_2) or 5 L/min or more via a nasal prong. When oxygen is delivered through a nasal prong, FiO_2 increases by approximately 4% for every additional liter of oxygen administered per minute [12]. According to a previous study on HFNC [9], early intubation was defined as tracheal intubation within 48 hours of initiating high-concentration oxygen therapy, and delayed intubation was defined as tracheal intubation 48 hours after initiation of high-concentration oxygen therapy.

Data collected on the index date (i.e., date of tracheal intubation) were age, sex, body mass index (BMI), comorbidities, and etiologies of respiratory failure. Pulmonary function data were collected on the day nearest to intubation. The GAP score that considers gender [G], age [A], and two pulmonary physiological parameters [P] (forced vital capacity [FVC, %] and diffusing capacity for carbon monoxide) was calculated using the method suggested by Ley et al. [13]; and the GAP stage was classified according to the GAP score (stage I, score 0–3;

stage II, 4–5; stage III, score 6–8). We reviewed the initial vital signs, laboratory findings within 24 hours before and after intubation, and duration of high-concentration oxygen therapy. Hypercapnic respiratory failure was characterized by a partial pressure of carbon dioxide in alveolar gas ($PaCO_2$) higher than 50 mm Hg. The ratio of oxygen saturation (ROX) index was defined as the ratio of pulse oximetry/FiO_2 to respiratory rate [14]. The parameters of mechanical ventilation within 24 hours of intubation were reviewed, and the median values of ventilator parameters were used for statistical analysis. Additional data collected during the ICU stay included use of adjunctive therapies such as vasoactive agents, inotropic agents, analgesics, sedatives, and neuromuscular blockers within 48 hours of tracheal intubation. Medical treatments in the ICU, including antifibrotic agents and systemic steroids, were reviewed. Steroid pulse therapy is defined as a short-term intravenous injection (usually 3 days) of high-dose (5–20 mg/kg) methylprednisolone or an equivalent dose of another steroid. Lung-transplant-free survival was defined as survival free of death or lung transplantation during hospitalization.

Study Outcomes

The primary outcome was the comparison of ICU mortality between early and delayed intubation groups in patients with IPF. The secondary outcomes were in-hospital mortality, 28-day mortality, and lung-transplant-free survival in the ICU and in-hospital. Data on ICU length of stay (LOS), hospital LOS, and discharge location to home or to other hospital were also collected.

Statistical Analysis

To minimize selection bias and control variables that might affect the results, we used the propensity score as a balancing score to adjust for confounding variables. This allowed accurate determination of the presence or absence of an association between timing of intubation and clinical outcome in patients with IPF [14,15]. The propensity score for timing of intubation was estimated using a multivariable logistic regression model with baseline covariates of age, gender, BMI, comorbidities, GAP stage, cause of respiratory failure, treatment for IPF, previous home oxygenation therapy, and Sequential Organ Failure Assessment (SOFA) score after intubation [14]. The early and delayed intubation groups were matched according to propensity score using a 1:1 nearest neighbor strategy without replacement and an optimal caliper of 0.1 standard deviation of the propensity score [15,16]. The quality of matching was assessed using the standardized mean difference, and matched patients were considered in the analysis of study results.

Baseline and clinical characteristics of patients with IPF according to timing of intubation were compared using the Wilcoxon rank-sum test for continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test. Clinical characteristics, laboratory findings before and after intubation, and parameters of mechanical ventilation after intubation were analyzed in the same way.

After propensity score matching, the Wilcoxon signed-rank sum test for continuous variables and McNemar's test for categorical variables were performed. Conditional logistic regression was used to evaluate the association between intubation timing and clinical outcomes with adjustment for key prognostic factors (age, SOFA score, and FVC). The propensity score model and the outcome regression model were combined to construct a doubly robust estimator that provides an estimation of the treatment effect for the primary outcome protected against possible model misspecification [17-19]. Statistical significance was set at $P<0.05$. Statistical analyses were performed using the R 4.0.2 software (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org) and Stata 13.1 software (StataCorp., College Station, TX, USA).

RESULTS

Baseline Demographics and Clinical Characteristics

During the study period, 173 patients with IPF were admitted to the ICU. After excluding 77 patients who were not intubated (n=15), intubated upon arrival (n=4), transferred after oxygen supplied or intubation performed at another hospital (n=11), admitted for lung transplant (n=21) or other surgeries (n=23), and younger than 19 years (n=3), 96 patients were included in this study (Figure 1). Before propensity score matching, 60 (62.5%) patients were in the early intubation group and 36 patients (37.5%) in the delayed intubation group. The baseline and clinical characteristics of the two groups before propensity score matching are shown in Table 1.

After propensity score estimation and matching in a 1:1 ratio, 33 matched pairs of patients were identified. The matched patients had a median age of 69 (interquartile range [IQR], 64–75), and most were male (n=48, 72.3%). Eight (12.1%) patients with IPF had a history of other respiratory diseases such as chronic obstructive lung disease, nontuberculous mycobacterial lung disease, or asthma. Acute exacerbation of IPF

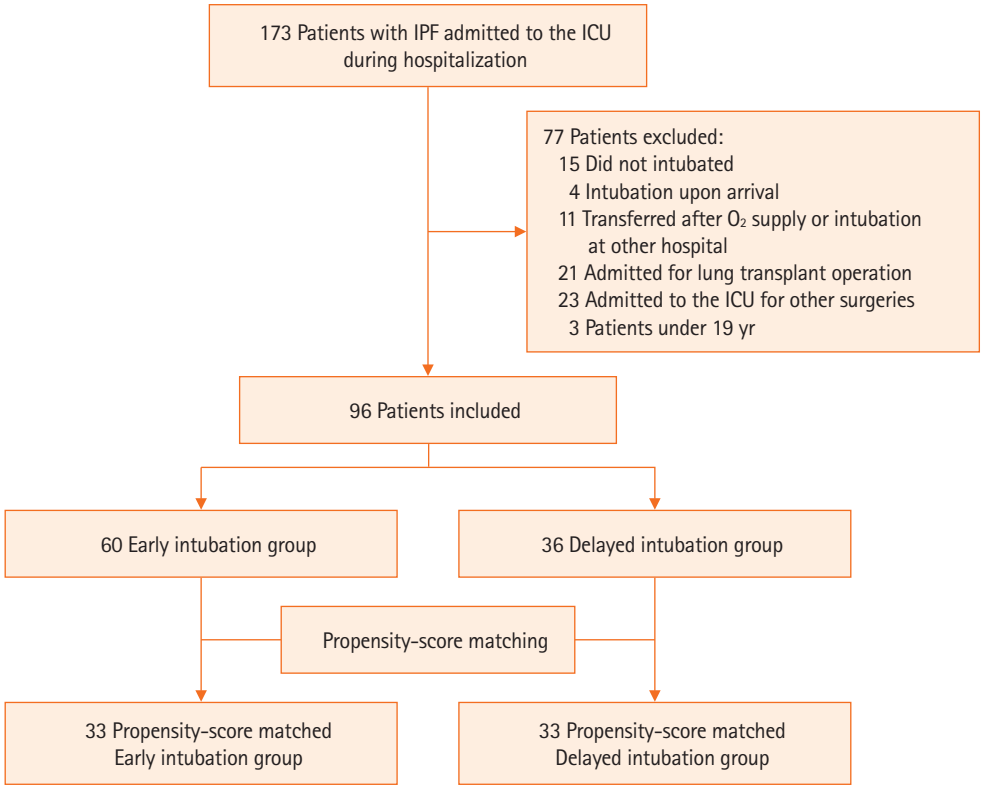

Figure 1. Flowchart of study patients. IPF: idiopathic pulmonary fibrosis; ICU: intensive care unit.

or pneumonia was the most common cause of hospitalization (n=59, 89.4%).

Oxygenation Therapy before and after Intubation

In the entire cohort, the median duration of high-concentration oxygen therapy before intubation was 0.5 days (IQR, 0.0–1.0) in the early intubation group and 5.1 days (IQR, 3.1–16.4) in the delayed intubation group. Total duration of oxygen therapy before intubation was longer in the delayed intubation group (13.1 days; IQR, 4.5–28.5) than in the early intubation group (1.1 days; IQR, 0.3–2.2) (P<0.001) (Table 2). Prevalence of home oxygen therapy maintenance before admission was 36.7% in the early intubation group and 41.7% in the delayed intubation group; the difference was not statistically significant (P=0.787). However, the median home oxygen flow was significantly higher in the delayed intubation group (3.0 L/min; IQR, 2.5–5.0) than in the early intubation group (2.0 L/min; IQR, 2.0–4.0) (P=0.040) (Table 2). After hospitalization, HFNC use was significantly greater in the delayed intubation group (80.6%) than the early intubation group (48.3%) (P=0.004) (Table 2).

Before intubation, $PaCO_2$ was significantly higher in the delayed intubation group (41.0 mm Hg; IQR, 36.8–50.2) than in the early intubation group (37.0 mm Hg; IQR, 32.3–42.5) (P=0.009) (Supplementary Table 1). Moreover, after propensity score matching, the proportion of hypercapnic respiratory failures before intubation was significantly higher in the delayed intubation group (28.1%) than in the early intubation group (10.3%) (P=0.025) (Supplementary Table 1). However, PaO_2/FiO_2 ratio and the ROX index were not significantly different between the two groups (P=0.442 and P=0.594, respectively) (Supplementary Table 1).

After tracheal intubation, there were no significant differences between the two groups in the initial mode of mechanical ventilation within 24 hours after intubation. However, after propensity score matching, the median positive end-expiratory pressure (PEEP) was significantly lower in the delayed intubation group, 5.0 cm H_2O (IQR, 5.0–7.0), than in the early intubation group, 8.0 cm H_2O (IQR, 7.0–10.0) (P=0.005) (Table 3). Minute ventilation was not significantly different, 11.2 L/min (IQR, 9.2–13.2) in the early intubation group and 12.8 L/min (IQR, 10.0–14.4) in the delayed intubation group (P=0.260). Saturation within 24 hours after intubation was 95% (IQR, 93%–97%) in the early intubation group and 95% (IQR, 92%–

Table 1. Baseline and clinical characteristics of patients with IPF according to the timing of intubation

Variable	Before matching			After matching		
	Early intubation group (n=60)	Delayed intubation group (n=36)	P-value	Early intubation group (n=33)	Delayed intubation group (n=33)	P-value
Demographics						
Male	42 (70.0)	28 (77.8)	0.553	23 (69.7)	25 (75.8)	0.593
Age (yr)	73 (68–77)	66 (60–75)	0.006	71 (68–75)	66 (61–75)	0.048
BMI (kg/m^2)	23.0 (19.5–25.1)	21.4 (19.3–24.1)	0.329	23.0 (20.7–25.4)	21.4 (19.3–24.1)	0.491
Cause of respiratory failure						
Acute exacerbation of IPF or pneumonia	54 (90.0)	33 (91.7)	0.999	29 (87.9)	30 (90.9)	0.655
Other diseases	6 (10.0)	3 (8.3)		4 (12.1)	3 (9.1)	
Comorbidity						
Cardiovascular disease	34 (56.7)	18 (50.0)	0.672	17 (51.5)	16 (48.5)	0.827
Other respiratory diseases	8 (13.3)	5 (13.9)	0.999	4 (12.1)	4 (12.1)	0.999
Diabetes mellitus	22 (36.7)	9 (25.0)	0.338	9 (27.3)	8 (24.2)	0.782
Chronic liver disease	3 (5.0)	0 (0.0)	0.289	0	0	-
Chronic kidney disease	10 (16.7)	3 (8.3)	0.359	3 (9.1)	2 (6.1)	0.655
Solid cancer	15 (25.0)	8 (22.2)	0.951	9 (27.3)	8 (24.2)	0.763
Hematologic cancer	2 (3.3)	0	0.526	1 (3.0)	0	0.999
Spirometry						
FEV_1/FVC	85.1 (79.7–88.1)	85.7 (81.9–90.7)	0.563	83.8 (79.7–87.2)	85.7 (81.9–90.7)	0.264
FEV_1 (% predicted)	68.0 (59.0–81.0)	67.5 (59.0–77.0)	0.834	67.0 (56.0–79.0)	67.0 (59.0–77.0)	0.525
FVC (% predicted)	57.0 (46.0–66.0)	55.0 (46.0–66.0)	0.902	55.0 (44.0–66.0)	53.0 (46.0–66.0)	0.427
DLco (% predicted)	40.5 (33.0–56.0)	41.0 (32.0–49.0)	0.730	43.0 (29.0–57.0)	40.5 (32.0–50.0)	0.370
GAP stage			0.147			0.422
Stage I	4 (7.0)	7 (20.6)		3 (9.1)	7 (21.2)	
Stage II	27 (47.4)	15 (44.1)		19 (57.6)	14 (42.4)	
Stage III	26 (45.6)	12 (35.3)		11 (33.3)	12 (36.4)	
Use of medication						
Anti-fibrotic agent	17 (28.3)	16 (44.4)	0.165	15 (45.5)	16 (48.5)	0.819
Glucocorticoid	13 (21.7)	13 (36.1)	0.192	9 (27.3)	11 (33.3)	0.564
Initial SOFA score	6.0 (4.5–7.0)	7.0 (5.0–8.5)	0.165	6.0 (5.0–7.0)	7.0 (5.0–8.0)	0.834

Values are presented as number (%) or median (interquartile range).
IPF: idiopathic pulmonary fibrosis; BMI: body mass index; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; GAP: gender, age, pulmonary physiological parameters; SOFA: Sequential Organ Failure Assessment.

98%) in the delayed intubation group (P=0.695) (Supplementary Table 2).

Clinical Outcomes in the Propensity-Matched Patient Groups

Before propensity score matching, ICU mortality was 56.7% (n=34) in the early intubation group and 75% (n=27) in the delayed intubation group, without significant difference (P=0.075) (Supplementary Table 3). However, after propensity score matching with adjustment for various confounding variables that may affect clinical results, ICU mortality was significantly higher in the delayed intubation group than in the early intubation group (adjusted odds ratio [OR], 3.99; 95% confidence interval [CI], 1.02–15.63; P=0.046) (Table 4). However, in-hospital mortality did not show a significant difference between the two groups, 75.8% in 25 patients in each group (adjusted OR, 1.08; 95% CI, 0.34–3.46). Additionally, there was no significant difference in 28-day mortality (adjusted OR, 1.39; 95% CI, 0.43–4.44) (P>0.05 for each).

More patients in the delayed intubation group (21.2%) received lung TPL than in the early group (12.1%); however, the difference was not significant (P=0.257) (Supplementary Table 4). The lung-transplant-free survival rate in the ICU was higher in the early intubation group (36.4%) than in the delayed intubation group (6.1%) (P=0.003). Furthermore, the lung-transplant-free in-hospital survival rate tended to be higher in

Table 2. Oxygen therapy before intubation, before and after propensity score matching

Variable	Before matching			After matching		
	Early intubation group (n=60)	Delayed intubation group (n=36)	P-value	Early intubation group (n=33)	Delayed intubation group (n=33)	P-value
Previous home oxygenation therapy						
By nasal cannula	22 (36.7)	15 (41.7)	0.787	15 (45.5)	15 (45.5)	0.999
Home O_2 flow (L/min)	2.0 (2.0–4.0)	3.0 (2.5–5.0)	0.040	2.0 (2.0–4.0)	3.0 (2.0–5.0)	0.457
By noninvasive ventilator	1 (1.7)	0	0.999	0	0	
O_2 delivery system before intubation						
Nasal prong	58 (96.7)	36 (100.0)	0.526	32 (97.0)	33 (100.0)	0.999
High-flow nasal cannula	29 (48.3)	29 (80.6)	0.004	20 (60.6)	26 (78.8)	0.133
Noninvasive ventilator	3 (5.0)	1 (2.8)	0.999	1 (3.0)	1 (3.0)	0.999
Duration of oxygen therapy before intubation						
Duration of low-concentration oxygen therapy (day)	0.0 (0.0–1.9)	0.0 (0.0–8.2)	0.158	0.0 (0.0–1.4)	0.0 (0.0–6.0)	0.074
Duration of high-concentration oxygen therapy (day)	0.5 (0.0–1.0)	5.1 (3.1–16.4)	<0.001	0.6 (0.2–1.0)	5.1 (3.5–16.9)	<0.001
Total duration of oxygen therapy (day)	1.1 (0.3–2.2)	13.1 (4.5–28.5)	<0.001	1.3 (0.3–2.2)	14.3 (4.8–29.4)	<0.001

Values are presented as number (%) or median (interquartile range).

Table 3. Comparison of oxygenation status and parameters of mechanical ventilation after intubation before and after propensity score matching

Variable	Before matching			After matching		
	Early intubation group (n=60)	Delayed intubation group (n=36)	P-value	Early intubation group (n=33)	Delayed intubation group (n=33)	P-value
ABGA within 24 hours of intubation						
Arterial pH	7.33 (7.24–7.37)	7.32 (7.26–7.35)	0.815	7.30 (7.21–7.37)	7.32 (7.26–7.36)	0.362
$PaCO_2$ (mm Hg)	47.5 (39.0–56.8)	48.8 (40.5–67.8)	0.427	51.0 (42.0–57.6)	49.0 (40.6–71.2)	0.538
PaO_2 (mm Hg)	82.9 (70.9–111.5)	86.5 (65.7–103.0)	0.771	79.0 (69.7–115.0)	86.0 (65.2–101.0)	0.879
FiO_2 (%)	80 (60–95)	90 (66–100)	0.194	80 (65–90)	80 (65–100)	0.566
PaO_2/FiO_2 ratio	115.5 (90.1–158.0)	98.3 (75.8–157.6)	0.300	116.2 (91.1–146.0)	99.7 (77.2–162.5)	0.846
Parameter of mechanical ventilator						
Initial ventilator mode			0.999			0.999
PCV	55 (91.7)	33 (91.7)		30 (90.9)	30 (90.9)	
VCV	1 (1.7)	1 (2.8)		1 (3.0)	1 (3.0)	
PSV	4 (6.7)	2 (5.6)		2 (6.1)	2 (6.1)	
Pressure support (cm H_2O)	20.0 (15.0–23.0)	22.0 (15.0–26.0)	0.047	20.0 (15.5–22.5)	22.5 (15.0–26.0)	0.171
PEEP (cm H_2O)	7.5 (5.0–9.0)	5.0 (5.0–7.0)	0.005	8.0 (7.0–10.0)	5.0 (5.0–7.0)	0.005
PIP (cm H_2O)	28.2 (24.0–31.0)	30.0 (25.5–31.5)	0.320	29.0 (26.0–32.0)	30.0 (26.0–31.0)	0.779
FiO_2 (%)	80 (60–100)	90 (66–100)	0.246	80 (65–90)	81 (65–100)	0.632
Tidal volume (ml)	407 (328–552)	432 (356–532)	0.639	400 (328–528)	432 (352–528)	0.865
Minute ventilation (L/min)	11.2 (8.4–14.1)	12.8 (9.6–14.4)	0.126	11.2 (9.2–13.2)	12.8 (10.0–14.4)	0.260

Values are presented as median (interquartile range) or number (%).
ABGA: arterial blood gas analysis; $PaCO_2$: partial pressure of carbon dioxide in alveolar gas; PaO_2: partial pressure of dioxide in alveolar gas; FiO_2: fraction of inspired oxygen; PCV: pressure-controlled ventilation; VCV: volume-controlled ventilation; PSV: pressure-supported ventilation; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure.

the early intubation group (15.2%) than in the delayed intubation group (6.1%) (P=0.299) (Table 4).

When ICU LOS was analyzed for 24 ICU survivors, there were no significant differences between the two groups, with a median of 12.0 days (IQR, 8.2–24.2) and 11.7 days (IQR, 9.9–17.9) in the early intubation and delayed intubation groups,

Table 4. Primary and secondary outcomes in the propensity-matched cohort

Variable	Early intubation group (n=33)	Delayed intubation group (n=33)	P-value	Adjusted OR[a] (95% CI)
Primary outcome				
ICU mortality	17 (51.5)	25 (75.8)	0.046	3.99 (1.02–15.63)
Secondary outcome				
In-hospital mortality	25 (75.8)	25 (75.8)	0.888	1.08 (0.34–3.46)
28-Day mortality from intubation	22 (66.7)	23 (69.7)	0.583	1.39 (0.43–4.44)
Lung transplant-free survival[b]				
In ICU	12 (36.4)	2 (6.1)	0.003	
In hospital	5 (15.2)	2 (6.1)	0.299	
Length of ICU stay (day)				
ICU survivor (n=24)	12.0 (8.2–24.2)	11.7 (9.9–17.9)	0.951	
ICU nonsurvivor (n=42)	7.1 (3.0–13.9)	7.6 (3.0–15.4)	0.868	
Length of hospital stay (day)				
In-hospital survivors (n=16)	84.9 (41.4–107.4)	57.5 (40.5–89.2)	0.401	
In–hospital nonsurvivor (n=50)	12.0 (3.5–21.4)	7.6 (3.0–15.4)	0.491	
Discharge (number/total)[c]			0.282	
To home	4 (50.0)	7 (87.5)		
To other hospitals	4 (50.0)	1 (12.5)		

Values are presented as number (%) or median (interquartile range).
OR: odds ratio; CI: confidence interval; ICU: intensive care unit.
a) Adjusted for age, Sequential Organ Failure Assessment (SOFA) score and forced vital capacity; b) Lung transplant-free survival was defined as survival free of death or lung transplantation during hospitalization; c) Analysis of surviving patients at discharge.

respectively (P=0.951). Additionally, there was no significant difference between the two groups when the hospital LOS of 16 in-hospital survivors was analyzed (early vs. delayed intubation group: 84.9 days [IQR, 41.4–107.4] vs. 57.5 days [IQR, 40.5–89.2], respectively, P=0.401) (Table 4).

DISCUSSION

In this retrospective propensity score-matched cohort study of patients with IPF, ICU mortality was significantly higher in the delayed intubation group, defined as tracheal intubation 48 hours after initiation of high-concentration oxygen therapy, than the early intubation group. However, there were no significant differences in in-hospital or 28-day mortality.

In recent studies, the in-hospital mortality rate of patients with IPF receiving mechanical ventilation was high, 50%–75% [20,21], but was lower than the previous report of 80%–90% [3,4,22]. In our study, in-hospital mortality of patients who received mechanical ventilation was 76%, similar to that of the recent results. For this reason, mechanical ventilation is not recommended in patients with IPF [1]. The potential extension of life offered by mechanical ventilation should be carefully weighed, particularly in IPF patients with worse prognostic factors, such as older age, decreased lung function, and pre-existing clinical frailty, and those with no further curative treatment options [20,23,24]. However, intubation may be considered in some patients with IPF when lung TPL is being considered. Nevertheless, the appropriate timing of intubation in patients with respiratory failure remains controversial.

Few studies have been conducted on the use of intubation in patients with IPF with respiratory failure. In a previous study, ICU mortality was significantly higher in critically ill patients who received delayed intubation more than 2 days after admission to the ICU (early vs. delayed intubation: 18.2 vs. 27.6%, P=0.007). Hospital mortality was also higher in patients with delayed intubation (23.4 vs. 33.3%, respectively, P=0.008) than in those with early intubation [25]. Furthermore, when HFNC was applied for respiratory failure and intubation was performed after HFNC failure, ICU mortality was significantly lower in early intubation (intubation within 48 hours of HFNC) than in delayed intubation (intubation after 48 hours of HFNC) (propensity-matched OR, 0.369; 95% CI, 0.139–0.984; P=0.046) [9]. In this present study, as in a previous study on patients with ARDS or respiratory failure, ICU mortality was significantly higher in patients with IPF who underwent delayed intubation at least 48 hours after high-oxygen concentration therapy.

HFNC is comfortable to use with humidified, warm air and provides a low PEEP effect. Some studies revealed that HFNC could reduce the intubation rate with acute hypoxemic respiratory failure [26,27]. Furthermore, high-concentration oxygen therapy is also maintained with nasal prongs or facial masks in clinical practice. However, considering the results of our and previous studies, delaying tracheal intubation after failure of high-concentration oxygen therapy in patients with IPF is not advised. This is particularly true for cases in which lung TPL is being considered. Spontaneous breathing before intubation in patients with acute respiratory failure may involve a high respiratory drive and large tidal volumes that lead to transpulmonary pressure swings [28,29]. Delayed intubation may exacerbate lung damage caused by spontaneous breathing in patients with IPF, which may lead to hypercapnic respiratory failure and increased ICU mortality.

Our data showed no statistical differences in in-hospital and 28-day mortality, which is consistent with a previous study in patients with HFNC failure [9]. However, although not statistically significant, in-hospital survival rate without lung TPL was higher in the early intubation group. The study may not have had sufficient power to detect a clinically important difference. Therefore, further studies with larger numbers of patients are needed.

Our study has several strengths. Lung function in patients with IPF significantly influences clinical prognosis [6]. In this study, actual data from pulmonary function tests was collected, and propensity score matching was performed considering the patient's lung function. Furthermore, this study included patients who received high-concentration oxygen therapy with nasal prongs, facial masks, and HFNC. HFNC has been widely used as an efficient oxygen supply in patients with respiratory failure. However, in actual clinical practice, nasal prongs and facial masks are also widely used due to lack of equipment, patient discomfort, and differences in in-hospital systems. Therefore, this study well reflects the actual clinical situation. However, there are study limitations to consider to properly evaluate the results. First, the number of patients was small because the prevalence of IPF was low, and the study was conducted in a single institution. Second, as this was conducted in a single tertiary university-affiliated hospital, selection bias may have been introduced. Third, the patients had multiple comorbidities, such as malignancy, which increased the severity of clinical outcomes. Fourth, since the oxygen concentration was calculated as FiO_2 4% per 1 L of O_2 in patients using a nasal prong or facial mask, the actual oxygen concentration may not be accurately reflected. Furthermore, due to the retrospective nature of the study, not all dependent variables were controlled. However, propensity score matching was used to control variables that may affect patient prognosis. Finally, the reason for tracheal intubation in IPF patients was not collected in our study. Further study on the indications for tracheal intubation as well as timing of tracheal intubation is needed.

In conclusion, in this study of patients with IPF that required mechanical ventilation, delayed intubation after 48 hours of high-concentration oxygen therapy was significantly associated with increased risk of ICU mortality compared with early intubation. Therefore, as with other causes of respiratory failure, tracheal intubation should not be delayed if needed in IPF patients who have failed high-concentration oxygen therapy, especially when lung TPL is being considered.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

ACKNOWLEDGMENTS

None.

ORCID

Eunhye Bae https://orcid.org/0000-0003-1362-7681
Jimyung Park https://orcid.org/0000-0003-2655-5517
Sun Mi Choi https://orcid.org/0000-0002-0742-6085
Jinwoo Lee https://orcid.org/0000-0003-0958-106X
Sang-Min Lee https://orcid.org/0000-0002-1388-9318
Hong Yeul Lee https://orcid.org/0000-0002-3638-8890

AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Data curation: EB. Formal analysis: EB, HYL. Methodology: all authors. Project administration: EB, HYL. Visualization: EB, HYL. Writing–original draft: EB, HYL. Writing–review & editing: all authors.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2022.00444.

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