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High-flow nasal cannula oxygen therapy to treat acute respiratory failure in patients with acute exacerbation of idiopathic pulmonary fibrosis

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Abstract

Background: Some patients with idiopathic pulmonary fibrosis (IPF) develop acute exacerbation (AE-IPF) leading to severe acute respiratory failure (ARF); despite conventional supportive therapy, the mortality rate remains extremely high. The aim of this study was to assess how a treatment algorithm incorporating high-flow nasal cannula (HFNC) oxygen therapy affects the short-term mortality of patients with AE-IPF who develop ARF.

Method and design: A retrospective cohort analysis was conducted.

Patients and interventions: The study consisted of 17 patients with AE-IPF admitted to a respiratory intensive care unit (RICU) for ARF managed using a treatment algorithm incorporating HFNC. The outcome measure was mortality rate during their stay in the RICU.

Results: Implementation of the treatment algorithm led to a successful outcome in nine patients and to a negative one in eight patients (47.1%) who died within 39 days of being admitted to the RICU. The survival rate was 70.6% (±0.1 %) at 15 days, 52.9% (±0.1%) at 30 days, 35.3% (±0.1%) at 90 days, and 15.6% (±9.73 %) at 365 days. Overall, 4 out of 10 patients who did not respond to conventional oxygen therapy showed a satisfactory response to HFNC.

Conclusions: Short-term mortality fell to below 50% when a treatment algorithm incorporating HFNC was implemented in a group of patients with AE-IPF admitted to a RICU for ARF. Patients not responding to conventional oxygen therapy seemed to benefit from HFNC.

The reviews of this paper are available via the supplementary material section.

Keywords: acute respiratory failure, high-flow nasal cannula, idiopathic pulmonary fibrosis, non-invasive mechanical ventilation.

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Introduction

Idiopathic pulmonary fibrosis (IPF), a chronic interstitial lung disease of unknown etiology, generally leads to a progressive decline in respiratory function and early mortality. Some patients may experience acute exacerbation (AE-IPF) during the course of the disease, leading to severe acute respiratory failure (ARF).[1] A recent international working group defined AE-IPF as 'an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality'.[2] Sharing several clinical features with acute respiratory distress syndrome (ARDS), AE-IPF may lead to severe, refractory hypoxemia.[3] In a limited number of cases, significant CO_2 retention, which is caused by the 'stiffness' of a fibrotic lung, may also occur.[4]

In the absence of proven beneficial therapies, clinicians may decide to prescribe supportive treatment to patients with AE-IPF who develop ARF in the attempt to normalize their ventilation and

oxygenation and thus to improve their clinical outcomes. But, despite conventional oxygen therapy and invasive or non-invasive ventilatory assistance, it is difficult to correct blood gas abnormalities; patient outcomes frequently remain poor with the majority dying within the first month and most of the remaining ones, within 1 year.[5,6]

One study reported prescribing venovenous extracorporeal membrane oxygenation (ECMO) as a rescue therapy to correct hypercapnia and respiratory acidosis in patients with IPF with severe hypoxemia who were responding neither to oxygen therapy nor to ventilatory assistance.[7] As the heart/lung support system proved unable to significantly improve the patients' in-hospital mortality, the authors concluded that it should be utilized only 'to bridge' patients to lung transplantation (LT).[8]

Some recently developed strategies to improve oxygenation and to reverse CO_2 retention have ameliorated the management of ARF in adult patients. High-flow nasal cannula (HFNC) oxygen therapy, which delivers heated, humidified inspired gas at a high flow rate and a precise fraction of inspired oxygen (FiO_2), is being increasingly utilized to correct severe, refractory hypoxemia in patients with respiratory distress due to a variety of causes. It has, in fact, been found to improve patients' oxygenation, respiratory rate (RR), heart rate, and dyspnea score.[5,9]

Extracorporeal CO_2 removal ($ECCO_2R$), a technique that uses a pump-assisted venovenous system to remove up to 25–30% of CO_2 production from the venous system, can, instead, be utilized as an adjunct to non-invasive ventilation (NIV) to avoid the need for invasive mechanical ventilation (IMV) and to prevent its potential complications. It has been found to be efficacious particularly in those with acute exacerbation of chronic obstructive pulmonary disease (COPD) or awaiting LT.[10]

To date, the only studies that have assessed the effect of these new technologies on the outcomes of patients with AE-IPF have been a case series showing that HFNC is well tolerated, leads to higher ventilation efficiency and lower RR, and reduces the work of breathing,[11] and a case report describing the successful utilization of an $ECCO_2R$ system as an alternative to tracheal intubation after NIV failure.[12]

The current study set out to assess the effect of a new treatment algorithm incorporating HFNC on the short-term mortality of a group of patients with AE-IPF who developed ARF. The study is based on data collected over a 5-year period during which time the treatment algorithm was utilized in the 17 patients with AE-IPF who were admitted to our respiratory intensive care unit (RICU) at the time they developed ARF.

Methods

This observational, retrospective cohort study was conducted in a tertiary teaching hospital located in northeast Italy. All the medical records of the IPF patients with AEs who were admitted to the four-bed RICU of the University of Padua Medical Center between 1 May 2013 and 30 April 2018 were collected and reviewed. The study was approved by the facility's Institutional Review Committee, and all the patients provided written informed consent forms, releasing their medical records for review.

Patients

All the patients previously or newly diagnosed with IPF using the multidisciplinary approach approved by the criteria proposed by the American Thoracic Society/European Respiratory Society consensus statement[1] and admitted to the RICU with AEs leading to the onset of ARF during the study period (1 May 2013 to 30 April 2018) were enrolled and retrospectively evaluated. Specific exclusion criteria were not adopted. In agreement with the recent recommendations of an expert panel, the diagnostic criteria for AE-IPF were the following: (1) previous or concurrent diagnosis of IPF; (2) acute worsening or development of dyspnea typically <1 month duration; (3) computed tomography (CT) scan showing new bilateral ground-glass opacity or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia; (4) pulmonary deterioration not fully explained by cardiac failure or fluid overload.[2] ARF was defined as an acute, rapid deterioration in respiratory function accompanied by an exacerbation of dyspnea over a few days associated with a deterioration in blood gas levels leading to hypoxemia [a PaO_2/fraction of inspired oxygen (FIO_2) ratio <250 mmHg].[13]

The following clinical and demographic features were reviewed: age; sex; smoking habits (the

patients were categorized as current, former, or never smokers); body mass index (BMI); the date of diagnosis and the length of time between the moment the disease was diagnosed and when the patient was admitted to the RICU; the number of respiratory-related hospitalizations the patient experienced during the year preceding admission; whether and for how long home oxygen or NIV therapy had been used; and whether the patient was on a waiting list for LT. The other data that were reviewed included: comorbidities that may have influenced the outcome measures, such as COPD, asthma, diabetes mellitus, cardiac disease (including cardiac arrhythmia, ischemic heart disease, or congestive heart failure), hematologic disorders, and chronic renal failure; pharmacological therapy, including corticosteroid monotherapy or immunosuppressive therapy (i.e. colchicine; cyclosporine A; azathioprine; combined corticosteroids, azathioprine, and acetylcysteine; interferon γ); pirfenidone; and nintedanib. All the records regarding the forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) and diffusing capacity for carbon monoxide (DLCO; single breath measurement corrected for hemoglobin) obtained from pulmonary function tests carried out over the 6 months preceding admission were likewise reviewed. Left ventricular ejection fraction (LVEF) and mean pulmonary artery pressure (mPAP) assessed using echocardiography carried out during the 3 months preceding admission were also reviewed. Pulmonary hypertension was defined as a resting mPAP $\geqslant$ 25 mmHg. A simple point scoring system (GAP index), a multidimensional prognostic staging system that estimates patients with IPF average mortality risk, was calculated based on these variables.[14]

The following parameters were recorded and analyzed at the time the patients were admitted to the RICU: RR, heart rate, body temperature, the Glasgow coma scale (GCS), arterial PaO_2, $PaCO_2$, and pH during spontaneous breathing with supplemental oxygen, PaO_2/FIO_2 ratio, leukocyte count, the N-terminal fragment of the prohormone of B-type natriuretic peptide (NT-proBNP), cardiac troponin, D-dimer, and serum C-reactive protein (CRP). A CRP serum level >100 was considered a risk factor for poor outcome.[15] The Acute Physiology and Chronic Health Evaluation score was also calculated.[16] A high-resolution CT (HRCT) of the lung was carried out and examined by a board-certified thoracic radiologist who evaluated the presence of new bilateral radiologic abnormalities (ground-glass opacification/consolidation). The patients' radiologic, hemodynamic, and laboratory test results were examined to investigate the possible causes of respiratory deterioration such as cardiac failure and fluid overload. Routine microbiological cultures of the bronchoalveolar lavage fluid samples, carried out in four of the patients, were also evaluated. Septic shock was diagnosed in accordance with the Surviving Sepsis Campaign 2008 Report guidelines.[17]

Supportive treatment

A treatment algorithm defined as a step-by step protocol for the management of a healthcare problem, in this case ARF in patients with AE-IPF, was developed.[18] Figure 1 illustrates the treatment algorithm utilized for ARF in our patients with AE-IPF admitted to the RICU; it included the interventions described as follows:

(a) Conventional oxygen therapy

Conventional oxygen therapy was initiated in the event that the patient showed severe hypoxemia ($PaO_2 < 60$ mmHg or oxygen saturation (SaO_2) $< 90\%$); oxygen therapy was delivered using an oxygen mask with a nonrebreathing valve and a reservoir bag; the oxygen setting was set to target a $SaO_2 \geqslant 92\%$;

(b) HFNC oxygen therapy

HFNC was utilized in hypoxemic patients who were not responding to conventional oxygen therapy or who were intolerant to an oxygen mask; inadequate response was defined as the inability to achieve a $SaO_2 \geqslant 92\%$. HFNC was delivered using a MR850 respiratory humidifier (Fisher & Paykel Healthcare, Auckland, New Zealand) including an air-oxygen blender, which makes it possible to achieve a precise adjustment of F_IO_2 (between 0.21 and 1.0) and to deliver an air/oxygen mixture at flow rates of up to 70 l/min through a heated humidifier. The gas mixture was routed through a circuit at a temperature of 37°C *via* large-bore bi-nasal prongs. HFNC was initially administered at a gas flow rate of 70 l/min and a F_IO_2 of 1.0; it was then adjusted to provide the minimum F_IO_2 necessary to maintain a $SaO_2 \geqslant 92\%$. Arterial blood gases (ABGs) were measured within 1 h after HFNC was initiated.

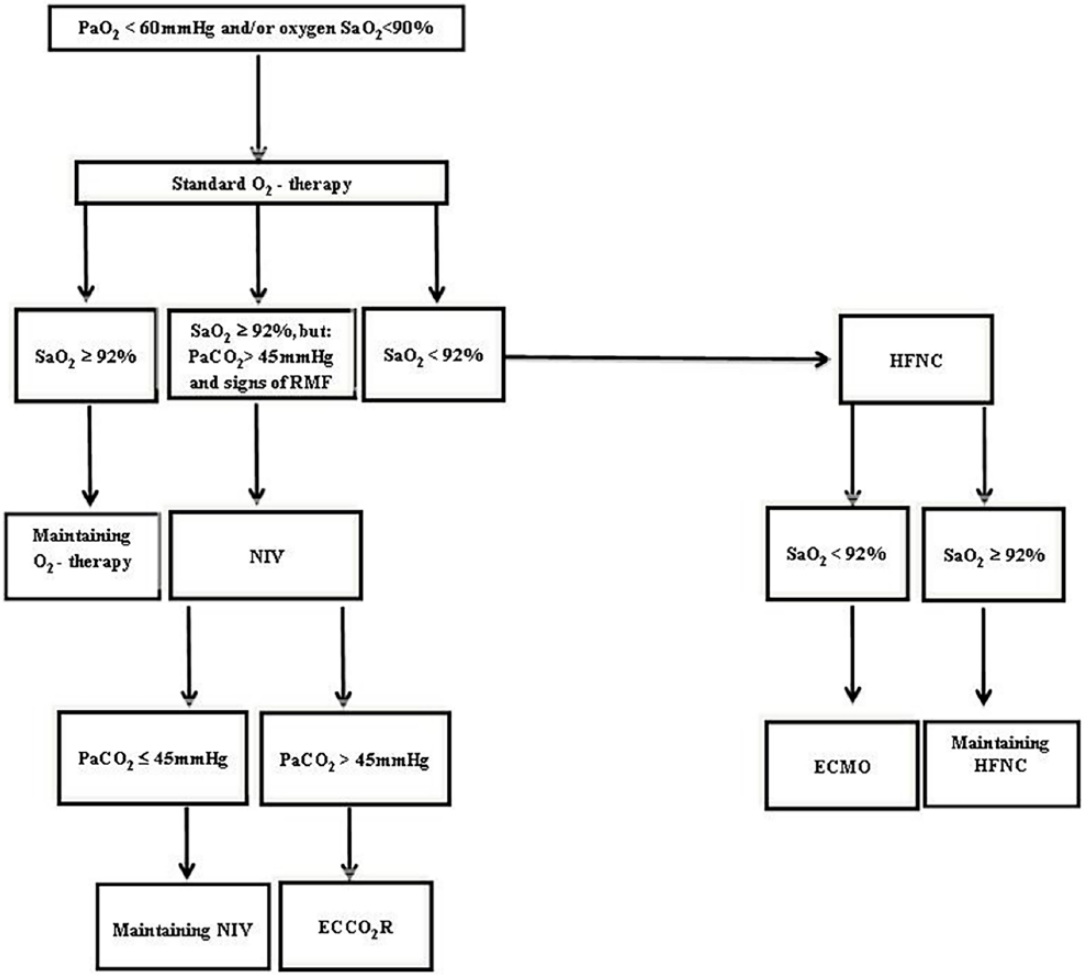

Figure 1. The treatment algorithm.
$ECCO_2R$, extracorporeal CO_2 removal; ECMO, venovenous extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; RMF, respiratory muscle fatigue; SaO_2, arterial oxygen saturation.

(c) NIV

In this particular RICU, NIV was initiated in any patients showing CO_2 retention ($PaCO_2 \geq 45$ mmHg) and signs of respiratory muscle fatigue (i.e. dyspnea, tachypnea, or abdominal paradox) after hypoxemia was reversed by means of conventional oxygen therapy or HFNC. NIV was delivered using a portable ventilator set on the pressure support (PS) ventilation mode. PS was initially titrated to a moderate tidal volume (6–8 ml/kg of ideal body weight); the ventilator setting was then readjusted depending on the ABG data in an effort to ensure a satisfactory, but not necessarily optimal, gas exchange while protecting the lungs from the risk of ventilator-induced lung injury (VILI). The PS levels did not exceed 25 cm H_2O. Positive end-expiratory pressure was usually set at 5 cm H_2O; the levels were raised by 1–2 cm H_2O without exceeding 6–8 cm H_2O given the high risk of pneumothorax. Supplemental oxygen was added to the ventilator circuit; the oxygen flow rate was set to achieve an arterial $SaO_2 > 92\%$ or $PaO_2 > 65$ mmHg. The NIV device employed in our RICU uses a full face mask.

(d) $ECCO_2R$

In the attempt to avoid IMV and its potential complications, $ECCO_2R$ was used to eliminate CO_2 from the blood of patients who remained hypercapnic ($PaCO_2 \geq 45$ mmHg) despite NIV administered at maximal tolerable ventilation pressures. The device used in our RICU (ProLUNG® system, Estor, Milan, Italy) is a

pump-driven venovenous system which utilizes a small, single venovenous dual lumen catheter (size = 13 Fr) that can be inserted into a femoral or jugular vein. It is characterized by a low blood flow rate (up to a maximum of 450 ml/min) and a single-use-only gas exchange cartridge consisting of a hollow fiber polypropylene diffusion membrane network with an effective surface area of 1.35 m^2. As the device uses a total volume circuit of only 120 ml, the hemodynamic impact on the patient is minimized. Blood flow can be adjusted depending on the ABG data in order to normalize the $PaCO_2$ level.

(e) ECMO

The decision to place a patient on ECMO was made by a team of specialists who evaluated the rapidity of lung function decline and the presence of hypoxemia, hypercapnia or acidemia despite maximum medical therapy and utilization of HFNC or ventilatory assistance or $ECCO_2R$. Patients not on a waiting list for LT were not considered for ECMO; those undergoing ECMO treatment were transferred to a specialized intensive care unit setting.

(f) IMV

Elective intubation and IMV following NIV failure were not situations that were considered by our treatment algorithm. Emergency intubation was carried out in the following conditions: respiratory arrest; loss of consciousness with respiratory pauses, gasping for air; heart rate $<$ 50 bpm with loss of alertness; hemodynamic instability with systolic blood pressure $<$70 mmHg.[19] IMV was delivered by an orotracheal tube using an intensive care unit ventilator set on the pressure control (PC) ventilation mode. PC was initially titrated to moderate tidal volume (6–8 ml/kg of ideal body weight); the ventilator setting was then readjusted depending on the ABG data in an attempt to ensure an acceptable, but not necessarily optimal, gas exchange, and to avoid VILI. Supplemental oxygen was added to achieve arterial $SaO_2 > 92\%$ or $PaO_2 > 65$ mmHg. The patients were usually sedated (midazolam at a maintenance dose of 0.02–0.2 mg/kg per hour) to reduce the distress potentially associated with the presence of a tracheal tube.

(g) Other treatments

All the patients received deep venous thrombosis and stress gastric ulcer prophylaxis. Patients with hypotension initially received intravenous fluid therapy with crystalloids. In the event hemodynamic instability persisted, vasoactive amines were initiated. High-dose corticosteroid therapy (1 mg/kg/day) and broad-spectrum antibiotic regimens were administered to all the patients throughout their stay in the RICU.

Electrocardiography, pulse oximetry, invasive or non-invasive blood pressure, and RR were continuously monitored.

The decision to begin supportive treatment was made by the attending physician in accordance with the patient and family's wishes after a frank discussion on its risks and benefits. Decisions about $ECCO_2R$ and ECMO treatments were reached by the multidisciplinary team made up of pulmonologists, thoracic surgeons, and anesthesiologists. ECMO treatment was considered an option available only to those patients awaiting LT.

Outcome measures and statistical analysis

The patients' relevant parameters both at the time they were discharged from the RICU and at the end of the follow-up period, the length of the stay in the RICU and the cause of death therein were analyzed. The mortality rate during the stay in the RICU was considered the primary study endpoint. Patients undergoing HFNC oxygen therapy were divided into two groups depending on their outcome: the 'success group' made up of the individuals who could be discharged from the RICU and were alive and conscious for at least 48 h after being transferred to a specialized respiratory ward and the 'failure group' made up of those who died during their stay at the RICU. The results are expressed, as appropriate, as mean values ± standard deviation, medians, and percentages. The Kolmogorov–Smirnov test was used to check the normality of the data distribution. The continuous variables were compared, depending on the normality of the distributions, using the Student's *t* test or the Mann–Whitney *U* test. Categorical variables were compared, as appropriate, using the chi-squared test or Fisher's exact test. Variables potentially useful in predicting RICU mortality were analyzed using the exact logistic regression model as the procedure can estimate a binary response variable even in the

event that the sample size is small;[20] the predictors of interest included all the data recorded in the charts. The variables with a $p \leqslant 0.1$ on univariate analysis were considered independent variables in the multivariate analysis. Survival from the time of admission to the RICU was calculated using the Kaplan–Meier method; potential predicting factors were analyzed as dichotomous variables using the log-rank test. The potential predicting factors were analyzed in the univariate analysis both as continuous and dichotomous variables. Cox's proportional hazard model was used in the multivariate analysis to analyze the patients' survival from the time of admission to the RICU as a time-dependent variable, and the variables with a p value of 0.1 or less at the univariate analysis as independent variables. Hazard ratios (HRs) are presented for the significant values.

All the calculations were carried out using MedCalc Statistical Software (Ostend, Belgium). A bilateral p value <0.05 was considered statistically significant for all the comparisons.

Results

The 17 patients who were admitted to our RICU between 1 May 2013 and 30 April 2018 with a diagnosis of AE-IPF were considered eligible to participate in our retrospective study. The patients' baseline demographic, clinical, pulmonary and cardiac function data are outlined in Table 1. There were approximately five-times as many males as females (14 *versus* 3); the median age was 67 years (51–89 years); and none were current smokers. A lung biopsy had been performed in six cases for diagnostic purposes. Overall, 4 patients had previously undergone immunosuppressive therapy, 10 were receiving pirfenidone and 1 had nintedanib treatment. In total, six patients had not been prescribed antifibrotic agents due to the following reasons: the drugs were not yet on the market (three cases; pirfenidone and nintedanib were, in fact, approved for IPF treatment by the regional health authority on 1 August 2013 and 1 April 2016, respectively); scarce compliance (two cases); the indications for the drug did not include the age group into which the patient fell (one case). Patient-reported comorbidities included the following: type 2 diabetes mellitus (five cases); ischemic heart disease (three cases); chronic renal failure (one case); atrial fibrillation (one case) and medullary aplasia (one case). Overall, 10 patients had been previously administered long-term oxygen therapy. There were four patients on a waiting list for LT.

The patients' clinical and laboratory data at the time they were admitted to the RICU are outlined in Table 2. Overall, four of the patients were pyretic; nine had leukocytosis (white cell count $>12{,}000 \times 10^6$/l) and four had serum CRP levels $>100\,\mu$g/ml. Also, two had high serum procalcitonin (PCT) levels (>0.50 ng/ml). Viral culture carried out on nasopharyngeal swab proved positive for type A and B influenza viruses in two patients. A total of eight (47.1%) responded in a satisfactory way to conventional oxygen therapy and hypoxemia was reversed; four of them were receiving long-term oxygen therapy. The other nine (52.9%), including six individuals on home oxygen therapy, required HFNC oxygen therapy. It was possible to discharge three out of the eight patients undergoing conventional oxygen therapy from the RICU: one suffered a sudden cardiac death and four were transitioned to NIV due to persisting CO_2 retention and dyspnea after hypoxemia was reversed. Out of the four patients having NIV, one was successfully discharged from the RICU, and one died from septic shock 24 days after undergoing emergency intubation because of acute, worsening hypercapnia causing severe hemodynamic instability. The patient in whom NIV proved ineffective was prescribed $ECCO_2R$, which reversed hypercapnia; he was discharged from the RICU on day 8. One patient was transitioned to HFNC oxygen therapy after $PaCO_2$ was normalized because of an intolerance to a conventional oxygen mask. Out of the 10 patients administered HFNC oxygen therapy (9 as a first-line intervention and one transitioned from NIV), 4 (including the one transitioned from NIV) responded satisfactorily and were discharged from the RICU. HFNC was unable to correct hypoxemia in the remaining six patients. After a frank discussion with each patient and his/her family, those concerned reached the decision to avoid tracheal intubation, given the poor outcome expectation. Although three out of six patients were on a waiting list for LT, the ECMO option was excluded after all relevant data was reviewed by our institutional ECMO team, given the poor prognosis due to comorbidities. All six patients died due to complications linked to severe refractory hypoxemia. Figure 2 illustrates the management and outcomes of the patients with AE-IPF.

Table 1. Patients' baseline demographic, clinical, and pulmonary-cardiac function characteristics.

	All patients (*n* = 17)
Age (years), median (range)	67 (51–89)
Sex (males / females)	14/3
BMI (kg/m^2), median (range)	23.8 (18.7–31.2)
Number of previous smokers	14
Length of time from diagnosis to RICU admission (years) median (range)	2.02 (0.17–5.01)
Number of hospitalizations earlier in the year, median (range)	0.00 (0.00–2.00)
Number of comorbidities, median (range)	2 (0–5)
Patients with previous cardiac disease (*n*)	4
Patients previously administered immunosuppressive therapy (*n*)	2
Patients previously administered pirfenidone (*n*)	10
Patients previously administered nintedanib (*n*)	1
Patients previously administered long-term oxygen therapy (*n*)	10
Patients previously administered long-term NIV (*n*)	1
Patients on waiting list for lung transplantation (*n*)	4
FVC, l median (range)	1.82 (1.15–2.75)
FVC, % median (range)	55.0 (21.0–101.0)
FEV_1, l median (range)	1.70 (1.09–2.66)
FEV_1, % median (range)	68 (41–120)
DLCO, ml/min/mmHg, median (range)	5.87 (2.91–7.90)
DLCO, % median (range)	28 (6–59)
Patients with PH (*n*)	12
GAP index, median (range)	5 (1–7)

BMI, body mass index; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; LVEF, left ventricular ejection fraction; NIV, non-invasive ventilation; PH, pulmonary hypertension; RICU, respiratory intensive care unit.

The overall RICU mortality rate of our study group was 47.1% (8/17). The mean duration of the follow-up period was 30.5 days [95% confidence interval (CI), 14.0–132.0]. All the patients falling into the failure group died within 39 days of being admitted to the RICU; the causes of death were: multiorgan failure with acute renal failure in six, septic shock in one, and cardiac arrest in one. The median RICU stay was 6 days (95% CI, 0–15). The median survival of the 17 patients after RICU admission was 35 days (95% CI, 14–137). The survival rate was 70.6% (±0.1 %) at 15 days, 52.9% (±0.1%) at 30 days, 35.3% (±0.1%) at 90 days, and 15.6% (±9.73 %) at 365 days (maximum length of the observation period) after RICU admission (see Figure 3). The stratified log-rank test showed that survival of the patients in the conventional oxygen therapy group

Table 2. Patients' clinical and laboratory data at RICU admission.

	All patients (n = 17)
Respiratory rate (breaths/min), median (range)	25 (16–42)
Heart rate (beats/min), median (range)	117 (58–170)
GCS median (range)	15 (14–15)
Patients with fever (n) (temperature > 38°C)	4
Patients with leukocytosis (n) (WBCs >12,000 × 10^6/l)	9
PaO_2 * (mmHg), median (range)	79.0 (34.0–258.7)
$PaCO_2$ (mmHg), median (range)	38.3 (25.3–65.9)
Arterial pH median (range)	7.44 (7.35–7.51)
SaO_2 (%) median (range)	92.0 (60.5–98.0)
PaO_2/FiO_2 median (range)	145 (46–289)
NT-proBNP (pg/ml) median (range)	1716 (44–6309)
Patients with abnormal NT-proBNP level (n)	7
Cardiac troponin (ng/ml), median (range)	2 (0.017–2799.0)
CRP (μg/ml), median (range)	33 (8.1–300.0)
Patients with CRP level > 100 μg/ml (n)	4
Patients with abnormal PCT level (n)	2
APACHE II score median (range)	20 (5–33)

***with supplemental oxygen.**
APACHE, acute physiology and chronic health evaluation; CRP, C-reactive protein; GCS, Glasgow coma scale; NT-proBNP, prohormone of B-type natriuretic peptide; PaO_2/FiO_2, arterial oxygen tension to inspired oxygen fraction ratio; PCT, procalcitonin; RICU, respiratory intensive care unit; SaO_2, arterial oxygen saturation; WBC, white blood cell.

did not significantly differ with respect to the HFNC group [median survival time: 133.0 (95% CI, 26.0–374.0) *versus* 21.0 (95% CI, 13.0–61.0) days; $p = 0.1323$; Figure 4].

The clinical and pulmonary function data at RICU admission of the patients undergoing HFNC oxygen therapy are outlined in Table 3. The six individuals who did not respond in a satisfactory way to treatment all had higher serum CRP levels [140 (8.1–300.0) *versus* 30.7 (9.4–36.0); $p = 0.088$] with respect to their counterparts. Exact logistic regression according to the multivariate analysis uncovered that none of the covariates had a significant effect on RICU mortality. Patient stratification according to their serum CRP levels at RICU admission revealed that median survival was significantly shorter in the patients with values above 100 μg/ml with respect to their counterparts with lower levels [11.0 (95% CI, 6.0–19.0) *versus* 39.0 (95% CI, 26.0–61.0) days], with an HR of dying of 3.785 (95% CI, 0.689–20.811; $p = 0.0240$).

Discussion

The current study aimed to evaluate the effect of a new treatment algorithm incorporating HFNC on

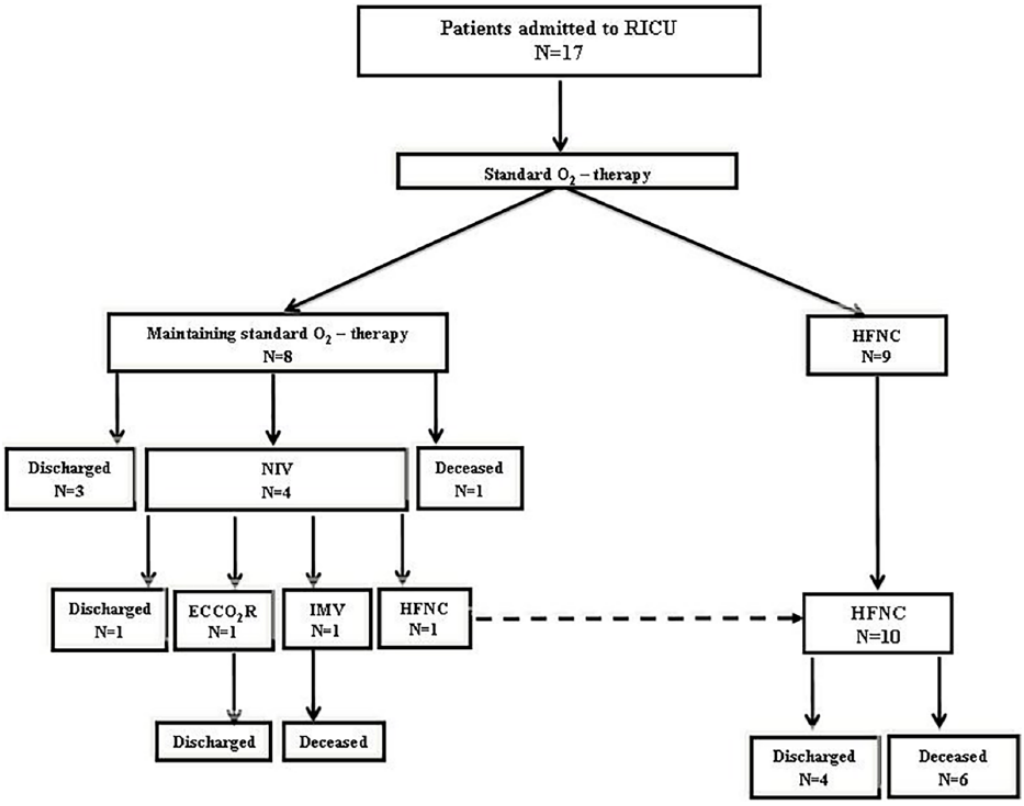

Figure 2. The study's flow diagram.
$ECCO_2R$, extracorporeal CO_2 removal; HFNC, high-flow nasal cannula; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; RICU, respiratory intensive care unit; SaO_2, arterial oxygen saturation.

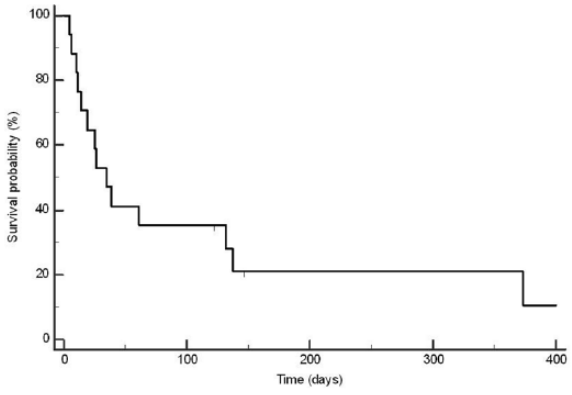

Figure 3. Kaplan–Meier estimates of survival function after RICU admission.
RICU, respiratory intensive care unit.

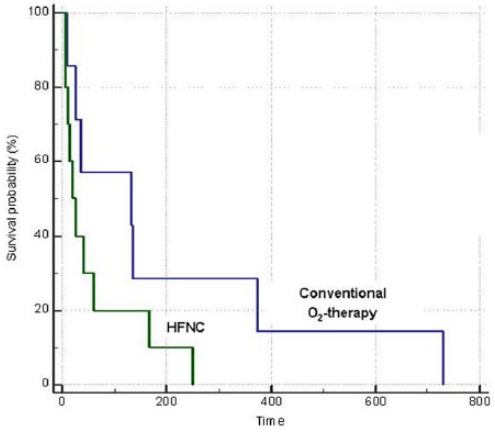

Figure 4. Kaplan–Meier estimates of survival function after RICU admission, stratified according to the type of supplemental oxygen therapy.
HFNC, high-flow nasal cannula; RICU, respiratory intensive care unit.

the short-term survival of a group of patients with AE-IPF admitted to a RICU because of ARF. The algorithm was used in place of previous therapeutic approach, based on conventional oxygen therapy, NIV in patients with CO_2 retention, and IMV in the event of NIV failure. The short-term mortality of this specific patient population reported by other studies has been exceedingly high, reaching approximately 90% prior to 2007[21]

Table 3. Clinical and laboratory data at RICU admission of patients undergoing HFNC oxygen therapy. The *p* values refer to differences between treatment success and treatment failure group.

	Treatment success group ($n = 4$)	Treatment failure group ($n = 6$)	*p* value
Age (years), median (range)	67 (52–79)	64 (51–84)	1.000
Sex (males/females)	3/1	6/0	0.400
BMI (kg/m^2), median (range)	24.87 (19.0–31.2)	24.6 (21.7–29.4)	1.000
Respiratory rate (breaths/min), median (range)	30 (25–42)	33 (28–39)	0.830
Heart rate (beats/min), median (range)	104 (80–110)	102 (88–120)	0.831
GCS median (range)	15 (15–15)	15 (15–15)	1.000
Patients with fever (*n*) (temperature $>$ 38°C)	1 (25%)	0 (0%)	0.400
Patients with leukocytosis (*n*) (WBCs $>$12,000 $\times$ 10^6/l)	2 (50%)	5 (83%)	0.500
PaO_2 * (mmHg), median (range)	69.85 (41.3–258.7)	80.6 (39.0–99.3)	0.831
$PaCO_2$ (mmHg), median (range)	37.7 (34.7–47.0)	38.0 (25.3–47.2)	0.830
Arterial pH median (range)	7.47 (7.45–7.51)	7.44 (7.40–7.48)	0.088
SaO_2 (%) median (range)	90.0 (74.0–98.0)	92.5 (70.0–97.0)	0.831
PaO_2/FiO_2 median (range)	147 (46–289)	143 (73–248)	0.831
NT-proBNP (pg/ml) median (range)	57 (55–1047)	91 (23–377)	1.000
Patients with abnormal NT-proBNP level (*n*)	1 (25%)	3 (50%)	0.571
Cardiac troponin (ng/ml), median (range)	152.5 (102.0–203.0)	2.0 (0.168–2799.0)	0.182
Serum CRP (μg/ml), median (range)	30.7 (9.4–36.0)	140 (8.1–300.0)	0.088
Patients with abnormal serum CRP level ($>$100) (*n*)	0 (0%)	4 (67%)	0.076
Patients with abnormal serum PCT level (*n*)	0 (0%)	2 (33%)	0.467
APACHE II score median (range)	28 (20–33)	19.5 (11–23)	0.043

*****with supplemental oxygen.
APACHE, acute physiology and chronic health evaluation; BMI, body mass index; CRP, C-reactive protein; GCS, Glasgow coma scale; HFNC, high-flow nasal cannula; NT-proBNP, prohormone of B-type natriuretic peptide; PaO_2/FiO_2, arterial oxygen tension to inspired oxygen fraction ratio; PCT, procalcitonin; RICU, respiratory intensive care unit; SaO_2, arterial oxygen saturation; WBC, white blood cell.

and touching 70% according to more recent studies.[22] Papiris and colleagues reported a mortality rate in 2015 of approximately 65% in a group of 17 patients with IPF, whose clinical and respiratory function characteristics were similar to those in our population, prescribed only conventional supportive care when they were hospitalized for AE; of note, avoiding steroids positively influenced survival.[23] As the RICU mortality rate found in our patients was 47.1%, the algorithm

outlined here seems to have had a positive effect on short-term prognosis, although survival remained low after they were discharged.

There are several factors that could explain why the treatment algorithm proved effective in improving the short-term prognosis of our patients with AE-IPF. First, HFNC appears to have played an important role in reversing hypoxemia in 40% (4 out of 10) of our patients who were unable to achieve sufficient oxygenation while they were using standard nonrebreathing face masks. Considering that severe hypoxemia caused by a marked ventilation/perfusion (V/Q) mismatch and impairment in the diffusing capacity is a predictor of poor outcome,[24] effective application of HFNC could have provided prognostic benefit to responders. Even if data on its utilization in patients with AE-IPF are limited, HFNC has the potential to improve oxygenation in patients not responding to conventional O_2 delivery systems. This may take place through a variety of mechanisms of action: first, it seems to provide a better matching of gas flow in individuals generating a high inspiratory flow, as in the case of patients with IPF,[25] by limiting the entrainment of room air during inspiration and ensuring higher FIO_2. Second, although delivered through an open system, HFNC creates a small continuous positive airway pressure that may provide positive pulmonary distending pressure and alveolar recruitment, although intrinsic recruitability has been found to be low in patients with IPF.[26]

When we examined the characteristics associated with HFNC failure, we found that elevated serum CRP levels at the time of RICU admission were associated with worse outcomes. Patients with CRP levels above 100 μg/ml were, in fact, found to have a substantially higher risk of HFNC failure (approximately four-fold) with respect to their counterparts with lower levels, and a significantly higher number of patients with abnormal CRP levels fell into the group with unsuccessful outcomes. In line with our results, a recently published retrospective study examining 169 patients with AE-IPF reported that CRP was the *only* independent predictor of hospital mortality.[27] Given the prognostic value of CRP, it is possible that inflammation rather than an accelerated intrinsic fibrotic process plays a decisive role in acute IPF progression.[28] Unexpectedly, the APACHE II score, a scoring system measuring disease severity in patients admitted to an intensive care unit did not have a significant prognostic value in patients administered HFNC.

In three out of the four patients who remained hypercapnic and fatigued following correction of hypoxemia, our algorithm, which is based on a stepwise utilization of NIV and $ECCO_2R$, was able to reverse CO_2 retention. Use of NIV has increasingly been found to be associated with beneficial effects in patients with AE-IPF leading to a lower rate of complications and death.[29–31] Given the high risk of complications linked to IMV, our algorithm offers $ECCO_2R$ as an alternative for those patients showing increasingly severe hypercapnia and clinical deterioration despite continuous use of NIV. The single patient who was prescribed this treatment showed a rapid decrease in $PaCO_2$ levels and a progressive improvement in clinical status over the first 3 days, making it possible to reduce NIV from continuous use to some breaks from ventilatory support. Considering that IMV does not seem to bring substantial benefits to patients with exacerbated IPF, the algorithm does not consider it an elective option for patients with CO_2 retention who are not responding to NIV treatment in view of the fact that the ICU mortality rate reaches approximately 90%.[32]

Finally, our treatment algorithm may have improved the short-term disease outcome in these patients because having a standard protocol to refer to during the management of such problematic patients may itself ameliorate the quality of care, as has been reported for similar, complex pathologies in the intensive care unit setting.[33]

Although our treatment algorithm *did* have a positive effect on RICU mortality, it did not, however, seem to affect the patients' long-term prognosis: the 1-year survival rate in our patients (15.6%) was similar, in fact, to the one reported by a recent study showing a survival rate of 13% in patients with IPF hospitalized for acute respiratory worsening.[34] In line with previous data, three out of four patients who were candidates for LT, all of which had been administered HFNC, died during the RICU stay, thereby confirming the high mortality rate of patients with IPF while on the waiting list for LT.[35]

Our study is characterized by some limitations: first and foremost, the limited number of patients enrolled. Of course, all clinical studies examining

patients with rare diseases such as IPF tend to present this limitation.[36] Moreover, since the study was retrospective, it was impossible to intervene in patient management as the attending physician was free to make all therapy-related decisions.

Conclusions

Despite its limitations, the study provides useful information for physicians staffing intensive care units and entrusted with the care of patients with exacerbated IPF. Its key findings can be summarized as follows:

- Use of a treatment algorithm incorporating HFNC can be associated with a short-term mortality lower than 50% in the event of ARF;
- HFNC should be provided to those patients who are not responding to conventional oxygen therapy as it seems to improve oxygenation in a relevant number of cases;
- Elevated serum CRP levels are a negative predictor of short-term outcome in patients treated with HFNC;
- The stepwise application of NIV and $ECCO_2R$ seems to reverse CO_2 retention after correction of hypoxemia and to avoid tracheal intubation in a significant proportion of cases.

In conclusion, although the treatment algorithm incorporating HFNC needs to be verified in a larger number of cases, the data outlined here provide encouraging results as far the short-term mortality of patients with AE-IPF in an intensive care unit setting is concerned.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Supplemental material

The reviews of this paper are available *via* the supplementary material section.

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