

Outcome of ventilation in patients with hypercapnic respiratory failure in IPF patients: A prospective study



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ABSTRACT

Background: Diffuse parenchymal lung disease (DPLD) is the inflammation and fibrosis of lung interstitium, resulting in respiratory failure. The rate of hypoxic respiratory failure is high as the disease progresses. In idiopathic pulmonary fibrosis (IPF) patients, acute deterioration leads to type 2 respiratory failure, etiology and management of which remains to be completely understood. **Aims and Objectives:** To identify the causes of type 2 respiratory failure and assess the outcome of invasive and non-invasive ventilation in patients with IPF. **Materials and Methods:** This prospective single center study included > 18-year-old 44 patients with IPF. History of patients, complete blood count, chest radiograph, urine routine, spirometry with bronchodilator reversibility, DLCO (diffusing capacity for carbon monoxide) testing, arterial blood gas measurements, and antinuclear antibody (ANA) test were evaluated. **Results:** Fourteen (31.8%) patients developed type 2 respiratory failure (within 1.5–6 years from the time of onset of illness). Causes of respiratory failure included acute exacerbation of IPF (35.71%), infections (14.29%), heart failure (14.29%), ischemic heart disease (14.29%), pulmonary embolism (21.43%), pneumothorax (7.14%), and surgical lung biopsy (7.14%). Patients were initiated on non-invasive mechanical ventilation (NIV) (64.29%) and invasive mechanical ventilation (IMV) (35.71%). Eight (88.89%) out of 9 patients on NIV survived, whereas all 5 patients (100%) on IMV expired. **Conclusion:** Considering the higher mortality rate associated with IMV, NIV is a better technique than IMV for improving patient outcome and management. NIV may be effectively implemented for improving the treatment outcome in patients with IPF and avoiding any aggressive therapeutic approaches.

Key words: Adolescent; Artificial respiration; Bronchodilator agents; Idiopathic pulmonary fibrosis; Interstitial lung diseases; Noninvasive ventilation; Respiratory insufficiency

INTRODUCTION

DPLD comprises of several group of diseases, which are characterized by inflammation of lung interstitium or parenchyma and varying degree of fibrosis.¹ The interstitium is stated as a region between the pulmonary vascular endothelium and alveolar epithelium that consists of several kinds of cells such as fibroblasts, myofibroblasts, macrophages along with extracellular matrix components including collagens, elastin, and proteoglycans.¹ Many patients

do not respond to treatment when oxygen capacity of lungs decreases drastically, and patients have difficulties in performing daily routine activities. Couple of decades back, DPLD was considered as a rare disease but now respiratory physicians encounter many cases of DPLD.¹ Manifestation of DPLD symptoms vary between patients. Around 200 etiological factors were identified for DPLD.² Interstitial lung diseases (ILD) can be broadly classified into four types: (a) disorders with known causes i.e., connective tissue disease including rheumatoid arthritis, systemic sclerosis, systemic

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lupus erythematosus, dermatomyositis or polymyositis and Sjogren's syndrome; (b) disorders with unknown causes i.e., idiopathic interstitial pneumonia (IIP); and (c) granulomatous ILD such as hypersensitivity pneumonitis and sarcoidosis, and (d) rare forms (LAM and LCH).³

The different causes of respiratory failure in IPF are acute exacerbation of DPLDIF, opportunistic infections in IPF, heart failure, ischemic heart disease, pulmonary embolism, pneumothorax, pulmonary hypertension, surgical lung biopsy, bronchial carcinomas, other causes including adverse effect of drugs, concomitant obstructive sleep apnea, concomitant chronic obstructive pulmonary disease etc.⁴ In India, earlier IPF was known as a rare disease, but this scenario has been changed over the few decades.⁵ Results of a prospective registry of ILD cases in India registered 1084 cases over a span of 3 years, 3 months (March 2012–June 2015) from 27 centers across 19 Indian cities. The prevalence of IPF has a 0.5–27/100,000 and an incidence of 0.22–8.8/100,000 inhabitants worldwide.⁶ Antifibrotic agents Pirfenidone and Nintedanib are approved drugs for IPF, while steroids can be useful during acute non-infective exacerbations. Lung transplantation is only hope for patients having progressive deterioration while on medical treatment.⁵ A better understanding of etiological factors, diagnosis and prognosis is required to develop management strategies to tackle IPF. The current research is one such initiative to know the various causes of the respiratory failure and its management in case of IPF.

MATERIALS AND METHODS

The patients were recruited from the Department of Pulmonology of Fortis Hospital, Vasant Kunj, New Delhi between May 2012 to May 2014. The study protocol was duly approved by Institutional Medical Ethics Committee (IMEC) and conducted in accordance with the Helsinki Declaration of 1975, as revised in 1983. The study was conducted after receiving the duly signed informed consent from all patients. Patients who are diagnosed cases of IPF as per ATS/ERS guideline 2011, aged above 18 years and those who were willing to give informed written consent were included in our study.

The detailed clinical history including respiratory complaints and duration, past medical history, family history and other illness was collected. The physical examination of the subjects was done. The subject's laboratory investigation included complete blood count, chest radiograph, urine routine and microscopic evaluation, spirometry with bronchodilator reversibility and DLCO testing, arterial blood gas measurements, and antinuclear antibody (ANA) test were performed. Patients who progressed

to respiratory failure were evaluated for different causes like acute exacerbation of IPF, infections, heart failures, ischemic heart disease, pneumothorax, pulmonary thromboembolism, pulmonary artery hypertension and Bronchogenic Carcinoma.

Sample size calculation

Sample size was calculated using the following formula:⁷

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where we expected respiratory failure in 70% of DPLD patients (p) = 70%, with a precision error of estimation (d) set at 0.14 (or 20% of p), alpha set at 0.05, the expected sample size was 40 cases.

Statistical analysis

The data was analyzed using (R software 3.1.2) SPSS 17.0. Continuous data were presented as mean \pm SD (standard deviation) and the categorical variables were presented as percentages with absolute numbers. The association between categorical variables was analysed using chi-square test or Fisher's exact test. Continuous data were compared using t-test. $P < 0.05$ was considered as statistically significant.

RESULTS

The study comprised of 44 subjects diagnosed with IPF including 28 females (63.64%). Majority of the subjects belongs to age group of 61 to 70 years (36.36%). Two patients (4.55%) had family history of IPF. Majority of patients in the sample presented with breathlessness (95.45%) and cough (81.82%). Two (4.54%) of the 44 patients were smokers. Three patients (6.8%) were ANA (antinuclear antibody) positive. As per chest radiograph findings, reticular shadows were identified in 38 (88.64%) patients and reticular shadows with honeycombing were observed in 5 (11.36%). DLCO in 40.91% of the sample was $< 60\%$, in 34.09% the capacity was between 60% and 80%, and in 20.45% of the sample, DLCO was $> 80\%$ (Table 1).

Fourteen patients (31.82%) presented with type 2 respiratory failure. The causes of type 2 respiratory failure were acute exacerbation of IPF in 5 patients (35.71%), infection in 2 subjects (14.29%), heart failure and ischemic heart disease in 2 patients (14.29%), pulmonary embolism in 3 patients (21.43%), pneumothorax in 1 (7.14%) patient, and surgical lung biopsy in 1 (7.14%) patient (Table 2).

All the 14 with type 2 respiratory failure patients were on ventilation, out of which 9 patients (64.29%) were on non-invasive mechanical ventilation (NIV) and 5 patients (35.71%) were on invasive mechanical ventilation (IMV).

Table 1: Demographic details of the study sample

Factors	Sub-category	Count (%)
Age group	<50 years	9 (20.45%)
	51–60 years	9 (20.45%)
	61–70 years	16 (36.36%)
	71–80 years	9 (20.45%)
	>80 years	1 (2.27%)
Gender	Female	28 (63.64%)
	Male	16 (36.36%)
Family History	Yes	2 (4.55%)
Symptoms	No	42 (95.45%)
	Breathlessness	42 (95.45%)
	Cough	36 (81.82%)
	Sputum	11 (25%)
	Chest pain	6 (13.64%)
	Hemoptysis	0 (0%)
	Wheeze	1 (2.27%)
	Other symptoms	27 (61.36%)
Smoking		2 (4.55%)
Clubbing		6 (13.64%)
Edema		7 (15.91%)
ANA status	Positive	3 (6.82%)
	Negative	41 (93.18%)
Chest X-ray findings	B/L reticular shadows	39 (88.64%)
	B/L reticular shadows with honeycombing	5 (11.36%)
DLCO	<60	18 (40.91%)
	60–80	15 (34.09%)
	>80	9 (20.45%)
Type 2 respiratory failure		14 (31.82%)

ANA: Antinuclear antibodies; DLCO: Diffusing capacity of the lungs for carbon monoxide

Table 2: Causes of type 2 respiratory failure

Causes (n = 14)	Count (%)
Acute exacerbation of IPF	5 (35.71%)
Infections	2 (14.29%)
Bronchial carcinoma	0 (0%)
Heart failure and IHD	2 (14.29%)
Pulmonary embolism	3 (21.43%)
Pneumothorax	1 (7.14%)
Surgical lung biopsy	1 (7.14%)
Other causes	0

IPF: Idiopathic pulmonary fibrosis; IHD: Ischemic heart disease

Eight out of 9 patients on NIV survived. All 5 patients on IMV expired (Table 3).

Mean pH (p=0.588), pCO₂ (p=0.861) and duration of illness (p=0.303) did not significantly differ between NIV and IMV groups (Table 4).

Table 5 presents the management modalities applied in the treatment of IPF patients.

DISCUSSION

DPLD comprises of a multiple group of diseases characterized by swelling of lung interstitium or parenchyma

Table 3: Association of outcome with type of mechanical ventilation

Type of ventilation	Total	Outcome	
		Survived	Expired
NIV	9 (64.29%)	8 (88.89%)	1 (11.11%)
IMV	5 (35.71%)	0 (0%)	5 (100%)

NIV: Non-invasive mechanical ventilation; IMV: Invasive mechanical ventilation

Table 4: Blood gas values in decompensated type 2 respiratory failure in idiopathic pulmonary fibrosis patients

Parameters	NIV	IMV	P Value
pH	7.26 ± 0.16	7.22 ± 0.062	0.588
pCO ₂	68.57 ± 26.52	70.78 ± 7.81	0.861
Duration of illness (years)	3.0 ± 1.34	3.80 ± 1.30	0.303

NIV: Non-invasive mechanical ventilation; IMV: Invasive mechanical ventilation

Table 5: Management modalities applied in the treatment of IPF patients

Modalities	Absolute numbers (%)
Steroids	24 (54.55%)
Antibiotics	8 (18.18%)
Diuretics	8 (18.18%)
Anticoagulants	3 (6.82%)
Intercostal tube	1 (2.27%)

and varying degrees of fibrosis. IPF is the commonest type of DPLD.⁸ The current research study was designed to identify the causes of type 2 respiratory failure and the treatment modalities applied to manage them.

In this study, most (36.36%) of the patients were in the age group of 61-70 years. A systematic review by Raghu et al concluded that frequency of IPF cases was increased with age and is reported frequently after 50 years of age.⁹ Most patients enrolled in the study were women (63.64%). Previous studies report higher incidence of IPF in men.¹⁰⁻¹² The 4.45% of the total study population had history of smoking. Case control study by Baumgartner et al reported 1.7-times increase in the chances of developing IPF and Simsek et al., observed 72% of IPF cases had a history of smoking while 63% in the control group were smokers.^{12, 13} It was observed that 4.5% of patients had family history of IPF. Familial IPF is associated with severe symptoms such as shortness of breath, tiredness, weight loss, and onset at younger age. Evidence of lung inflammation has also been observed in unaffected family members of those with familial IPF. These results present compelling evidence supporting the existence of genetic factors that predispose to IPF.¹⁴ However, specific genetic factors of IPF are not known.

In this study, 13.6% and 15.9% of the total study population presented with clubbing and edema, respectively, which

were in concordance with the existing literature.^{15,16} Most common abnormality seen in IPF patients was reticular abnormality (pattern seen on the chest radiograph) and it was reported that honeycombing (patches of cystic spaces in lungs) develops in later stages of disease. Our study found bilateral reticular shadows in about 88.6% patients and 11.4% patients had bilateral reticular shadows along with honeycombing. Maheshwari et al reported identification of reticular shadows in the chest X-ray of 92% patients with IPF.¹⁷ Kundu et al., reported identification of reticular shadows in the chest X-ray of 100% patients with IPF.¹⁸ A study by Wyuts et al., concluded that 67% of patients with IPF had honeycombing.¹⁹

About 32% (14 patients) developed type 2 respiratory failure and the causes were acute exacerbation of IPF (35.71%), pulmonary embolism (21.43%), heart failure (14.29%), infections (14.29%), pneumothorax (7.14%), and surgical lung biopsy (7.14%). Smith et al 2021 reported pneumonia (56.3%), IPF exacerbation (62.5%), cardiac disorders (25%), pulmonary embolism (2.1%), sepsis (8.3%), and others (8.3%) as reasons of respiratory failure.²⁰

Moreover, patients were treated with steroids (54.5%), diuretics (18.2%) and antibiotics (18.2%), anticoagulants (6.8%) and intercostal tube drainage (2.3%) for the treatment of type 2 respiratory failure. Smith et al 2021 reported the use of steroids (79.2%), vasopressors (14.6%), and hemodialysis (4.2%).²⁰

Furthermore, all 14 patients with respiratory failure were on artificial ventilation, out of which 9 patients (64.29%) were on NIV and 5 patients (35.71%) were on IMV. Eight out of 9 patients on NIV survived. All 5 patients on IMV expired. Luo et al 2020, investigated the clinical outcomes of mechanical ventilation. Similar results on mortality rates associated with NIV and IV ventilation were reported (62% vs 88%).²¹

This study summarizes the etiology of type 2 respiratory failure in IPF patients and management strategies to treat complications of IPF. The study has a few limitations. It was a single-center study. Other limitations include a small sample size and a referral bias. Patients referred from a specialized center tend to have complex presenting features and that could have affected prognosis of patients.

CONCLUSION

Patients were treated with steroids, diuretics, antibiotics, anticoagulants, and intercostal tube drainage based on, underlying etiology. Considering the higher mortality rate associated with IMV, the study concludes that NIV is a

better technique than IMV for improving patient outcome and their overall management. NIV may thus be effectively used and further modified for improving the treatment outcome in patients with IPF and avoiding any aggressive therapeutic approaches.

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MHK- Concept and design of the study; prepared first draft of manuscript; **PKT-** Interpreted the results; reviewed the literature and manuscript preparation; **VN-** Concept, coordination, review of literature and manuscript preparation; **RSC-** Statistically analyzed and interpreted, preparation of manuscript. All authors revised and approved the manuscript.

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