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Clinical outcomes following enhanced respiratory support in ILD Patients with acute Respiratory failure

Andrew Achaiah[1], Matthew Quint[2], Olivia Bird[3], K. Suresh Babu[4]
[1](Respiratory registrar, Respiratory Department, Basingstoke and North Hampshire Hospital, Basingstoke, UK)
[2](Senior Physiotherapist, Respiratory Department, Queen Alexandra Hospital, Portsmouth, UK)
[3](Junior doctor, Respiratory Department, Queen Alexandra Hospital, Portsmouth, UK)
[4](Respiratory consultant, Respiratory Department, Queen Alexandra Hospital, Portsmouth, UK)
Corresponding author: Andrew Achaiah1

Abstract: *The outlook for patients with ILD presenting to hospital needing respiratory support is poor be it non-invasive ventilation or mechanical ventilation. Based on the available evidence it is difficult to determine a clear role for NIV in patients with ILD. We undertook a retrospective analysis of patients with ILD admitted with acute respiratory failure requiring enhanced respiratory support. We intended to evaluate the outcome from enhanced respiratory support and to ascertain the variables that portend prognosis.*
54 patients with a median age of 75.8 (±1.29) and a diagnosis of ILD needed enhanced respiratory support. 65% were male. Mortality for patients admitted to RHDU was 67%. 7% of patients died within 30 days of discharge, 9% died within 3 months and 11% survived beyond 1 year from admission. Time from diagnosis to presentation with ARF was significantly greater in the deceased group, median duration 18.7 (±3.76) vs. 8.5 (±9.33) months in the survivors (p=0.047). There was no difference in lung function, admission arterial blood gas or biochemistry. 43% of patients had IPF; 83% died during their stay.
The mortality for patients with ILD admitted for ARF is high and early decisions for escalation of care is critical in making treatment decisions.

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I. Introduction

Interstitial lung disease (ILD) is an umbrella term used to describe pulmonary disorders involving the lung parenchyma that occur due to known or unknown causes1. Acute respiratory failure (ARF) is a known complication of ILD which can be triggered by infections, pulmonary embolism or heart failure. When no obvious precipitant is found, the term acute exacerbation of ILD is used.2In such circumstances, patients are considered for respiratory support in the form of non-invasive (NIV) and/or mechanical (MV). General consensus is that outcome of MV in ARF for this population is poor.3A systematic review examining 9 observational single centre studies reported a 87% in-hospital mortality for patients with IPF receiving MV.4 The short-term mortality i.e. mortality within 3months of hospital discharge was 94%.

NIV has been recognised as an option to avoid intubation during ARF in patients with ILD to reduce the complications especially ventilator associated infections. It has been a valuable option in patients unsuitable for MV, and also in rapidly progressive interstitial pneumonia if offered early.5This study showed that early intervention was a significant predictor of survival at 30 days. The outcome from NIV varies from patient to patient due to the heterogenicity of the ILD. Hence the outcome will depend not only on the aetiology of ILD but also on the cause of the recent deterioration.

In this retrospective observational study, we evaluated clinical outcome in patients with a diagnosis of ILD presenting with acute respiratory failure requiring non-invasive respiratory support. We attempted to gauge the predictors of outcome to understand if any particular subgroups or physiological parameters can influence our decision for potential enhanced respiratory support.

II. Methods

Study design

We conducted a retrospective analysis of short-term outcome in patients with a diagnosis of ILD with acute respiratory failure requiring admission to our 10-bedded Respiratory High Dependency Unit (RDHU) for non-invasive respiratory support. The study was approved by the Institutional Review Board (Portsmouth Hospitals NHS Trust Ref No: 3578/2016). Patients were identified through searching the RHDU electronic data base and their medical records. 54 patients were identified between January 2012 and December 2016 with ILD needing enhanced respiratory support.

Data was collected on patient demographics, time of diagnosis of ILD and duration, associated respiratory and non-respiratory co-morbidities, pulmonary function tests (PFTs), admission arterial blood gas (ABG) values, blood biochemistry and counts, type and duration of non-invasive respiratory support used and clinical outcomes. A thoracic radiologist with a sub-specialty interest in ILD reviewed each patient's cross-sectional imaging to provide a radiological diagnosis that fits with the patients' clinical description.
The primary outcome was survival from hospital admission. Secondary outcomes included mortality at 30 days, 90 days and survival past one year. Survival data was correlated with the ILD subtype, disease severity, length of stay on RHDU, ABG and biochemical parameters. The factors were then compared between the groups.

Indication for non-invasive respiratory support was acute respiratory failure. Type I acute respiratory failure was defined as patients with an admission pO2<8.0kPa and type 2 respiratory failure as pO2<8.0kPA and pCO2>6.7kPa. Methods of respiratory support included Nasal High Flow Oxygen (NHFO), Continuous Positive Airways Pressure (CPAP) and Bi-level Positive Airway Pressure (BiPAP).Specific ventilator support settings and pressures were not explored. Medical treatment was administered depending on the trigger for ARF and in accordance with local treatment guidelines.

Study definitions

A UIP (usual interstitial pneumonia) pattern on HRCT thorax imaging was defined by the presence of a basal-predominant sub-pleural reticular abnormality and honeycombing with or without traction bronchiectasis. A NSIP (non-specific interstitial pneumonia) pattern was defined by the presence of ground-glass opacification in a peripheral, sub-pleural distribution with or without consolidation. Hypersensitivity Pneumonitis (HP) or Extrinsic Allergic Alveolitis (EAA) was defined as ground-glass change, mosaic attenuation and possibly honeycombing in an upper lobe predominance on HRCT. RA-ILD (Rheumatoid arthritis) was defined as UIP pattern on HRCT as a manifestation of connective tissue disease in patients with rheumatoid arthritis. Pneumonia was defined as the presence of new consolidation of chest x-ray or CT chest associated with new or increased cough with or without sputum production, pyrexia with abnormal white cell count and / or elevated inflammatory markers namely C-reactive protein. An acute exacerbation of ILD was defined as an acute and clinically significant deterioration in physiological parameters, gas exchange or new radiographic opacities in the absence of other explanations including infection, PE, left ventricular failure or pneumothorax.

Statistical analysis

Data collected was entered on Microsoft Excel. Descriptive statistics were used to analyse physiological parameters. Continuous data was expressed as median values (± standard error). Categorical data is expressed as counts or percentages. Patient characteristics and physiological parameters were compared between two groups; Death or survival upon admission to RHDU. Difference between groups were analysed using non-parametric test (Mann-Whitney U) and a p value <0.05 was considered significant.

III. Result

54 patients with a diagnosis of ILD were identified needing enhanced respiratory support. 35 (65%) patients were male and 19 (35%) were female with a median age of 75.8 (±1.29). 35% (19/54) received BiPAP, 35% (19/54) had CPAP and 30% (16/54) had HFNO as enhanced respiratory support during their stay in the respiratory high care unit.66% (35/54) of patients presented with type 1 respiratory failure. The median duration from diagnosis to presentation with ARF was 15.4 ±3.89 months. The proportions of these co-morbidities were similar between the two groups.

The mortality for patients admitted to RHDU was 67% (36/54). The mean length of stay for the deceased group was 3 ± 0.95 days while for the survivors this was 4.5 ± 2.65 days (p=0.058). A further 4 (7%) patients died within 30 days of discharge, 5 (9%) died within 3 months of discharge and 3 (6%) died within 12 months (6%) patients. Only 6 patients (11%) survived beyond 1 year from admission to RHCU. Baseline demographics are shown in table 1.

Median length of stay in RHDU was 2 days (±0.35) in the deceased group compared to 4.5 days (±2.65) in those who survived (p=0.058).The time from diagnosis of ILD to presentation with ARF was found to be significantly greater in the group of patients that died with a median duration of 18.7 (±3.76) months compared to 8.5(±9.33) months in the survivors (p=0.047). This could indicate progression of disease.

Evaluating the most up-to-date PFT, there was no statistical difference in FEV1 (Forced Expiratory Volume in 1 second), FVC (Forced Vital Capacity) or TLCO (Diffusing Capacity for Carbon monoxide) between the two groups. There was no difference in admission blood pH, PO2 or PCO2 between groups. The lung function, blood gas on admission and blood counts are summarised in the table 2. 66% (35/54) were in T1RF on admission to RHDU and 34% (18/54) were in T2RF. 19 (35.2%) patients received BiPAP, 16 (29.6%) received HFNO and the remaining 19 (35.2%) had CPAP as the modality of enhanced respiratory support during their stay in the RHCU. Median duration on respiratory support was 24 hours (±7.3) in the group of

patients who did not survive while for the survivors this was 36 hours (±17.1);p=NS. Patients admitted with ILD had various respiratory and non-respiratory co-morbidities which are presented in table 3.Positive microbiology results were identified in 11 patients (20%) of which 7 patients died during their hospital stay. Use of long-term oxygen therapy was present in 21 patients (39%). 13 of these patients (62%) did not survive.

Examining the sub group of patients based on the types of ILD diagnosis and associated predictive factors for mortality based on their diagnosis, IPF was diagnosed in 23/54 (43%), HP in 6/54 (11%) and NSIP in 6/54 (11%). The distribution of the types of ILD and their outcome following admission to RHDU is shown in Table4. Patients with IPF constitutes a significant proportion of admissions to the RHDU for enhanced respiratory support of the 23 patients with IPF (male 70%; mean age 74.0 ±8.9) admitted for respiratory support 10 patients received CPAP, 6 received high flow nasal oxygen and 7 received NIV. 19 (83%) patients died during hospital stay. 1 patient died 22 days after discharge. 30-day mortality was 87% (20/23); 3 patients survived beyond 30 days and all patients died within 3 months of their admission with ARF. There was no difference between groups in age, sex, lung function (FEV1, FVC, and TLCO) and admission blood gas parameters (pH, PO2, PCO2). Time from diagnosis to presentation with ARF was higher in the 30-day mortality group (24.3 months ± 4.9) compared to the survival group (3.3 months ±1.8); p=Not significant.

IV. Discussion

Our review of patients with ILD needing enhanced respiratory support in the form of HFNO, CPAP or BiPAP illustrates the poor outcome in this group. To the best of our knowledge there are currently no randomised controlled trials evaluating the efficacy of NIV in patients with ILD undergoing an episode of ARF. Despite there being a dearth of data on this topic, NIV is commonly used to treat an acute deterioration in patients with ILD[1]. Furthermore, NIV use in this sub-group of patients is increasingly considered as an initial treatment option for ARF and as a way of delaying / deferring mechanical ventilation and several studies have demonstrated high mortality rates when proceeding to endotracheal intubation and mechanical ventilation.[6-8]

There are very few studies that have evaluated outcome of the use of NIV in patients presenting with ARF, with pre-existent ILD. Given the heterogeneity of ILD in terms of both pattern of disease behaviours and underlying aetiology, identifying the patients that would be suitable candidates for trial of NIV from the general ILD population is vitally important in the management of all ILD patients with ARF. A study by Güngör et al showed that the mortality rate for patients with ILD initially receiving NIV was 42.6%.[9]One of the purposes of our study was to identify any markers and parameters that were significantly different between the two groups of patients (deceased vs. survival from RHDU admission) with the notion that any differences may identify predictors of poorer outcome. Our data did not identify any significant differences in pre-admission PFTs, blood biochemistry or arterial blood gas analysis that could be used to predict outcome between the two groups. Increased duration of disease was shown to be associated with poorer outcome and increased chance of hospital mortality in a presentation with ARF requiring NIV. Median diagnosis duration 18.7 months (death) vs. 8.5 months (survive), p=0.047. RHDU length of stay was greater in the group of patients that survived; median duration 4.5 days (±2.65) vs. 2 days (±0.35). Although not statistically significant (p=0.058), this may reflect the severity of disease and concomitant deterioration in patients that died and / or the additional time required to respond to treatment. These results are similar to the one reported by Güngör.[9] They identified that an APACHE score >20 and continuous NIV demand were significant risk factors for NIV failure.

In our study, treatment of IPF with NIV on RHDU was met with 83% mortality.3 month mortality was 100%. Kaplan Meier survival curves (Fig. 1) for patients grouped as IPF and Non-IPF shows that a diagnosis of IPF is associated with a higher mortality and a non-IPF diagnosis is associated with a mean survival of 14.4 weeks (CI 6.5-22.2) following admission to RHCU. Survival beyond 1 year from RHDU admission was 11%in our cohort of patients. Mallick et al reviewed several reports on the outcome of patients with IPF who received MV and showed that this was a futile exercise.[4] The study concluded that out of 135 patients 94% died within 3 months of hospital discharge. Hence the official ATS/ERS/JRS and ALAT statement recommends that patients with IPF should not receive mechanical ventilation.[10] It is speculated that NIV is an option for ARF in patients with ILD as it reduces endotracheal intubation and ventilator associated pneumonias.

The most common respiratory co-morbidity observed in our study was pneumonia. This was present in 29 cases and fatal in 20 cases (69%). It was present in 12/ 23 cases of IPF, 9 (75%) of which were fatal. When the frequency of a pneumonic presentation was split per ILD sub-type it was most commonly seen in patients with IPF (12 patients, 52%), RA-ILD (4 patients, 80%) and NSIP (5 patients, 83%). In IPF acute infection is second only to acute exacerbation as a cause of rapid progression.[11]Huie and colleagues while doing a detailed diagnostic evaluation of patients with fibrotic lung disease and acute respiratory decline identified infectious aetiology in one third of patients, however this did not have an effect on the outcome for these patients.[12]Our data suggests that pneumonia has both a considerable impact on the patient's initial presentation and in terms of their outcome.

The most frequent non-respiratory co-morbidity found was cardiovascular involvement. Cardiovascular co-morbidity was found in 33 patients (61%). The most common findings being structural heart disease (22%), hypertension (20%) and ischaemic heart disease (19%). Of these, ischaemic heart disease had the highest in-hospital mortality rate of 80%. The presence of pulmonary hypertension has been described in previous studies as an independent risk factor for mortality in ILD patients presenting with ARF.[6] In our study pulmonary hypertension was present in 4 patients. 2 of these patients did not survive. The highest burden of cardiovascular involvement was seen in the IPF cohort of patients, this cohort of patients also had the greatest mortality rate. A recent study by Kreuter and colleagues have identified that lung cancer and cardiac disease as significant predictors of death in patients with IPF.[13]

T1RF was more commonly seen than T2RF, and proportionately was seen with greater in-hospital mortality (25 patients, 71%) in comparison to T2RF (11 patients, 61%). For patients in T1RF, CPAP appeared to be the favoured mode of treatment compared to High-flow nasal oxygen (19 patients vs. 16 patients). However, survival was much greater in patients receiving high flow nasal oxygen (50%) in comparison to CPAP use (17%). While these were not statistically significant due to small numbers in the groups, use of high flow nasal oxygen to treat T1RF is becoming more popular in critical care settings.[14]The potential reasons for this it appeared to be that patients receiving nasal high flow oxygen presented at a later time within the study; from July 2014 onwards, potentially at a time when high-flow nasal oxygen was phased in as a treatment option for T1RF on our RHDU. This may reflect better tolerability to use of nasal-high flow oxygen, as has been seen in other studies.[7,15] While our understanding of HFNO is still in investigational stages especially in the context of ARF in ILD, a recent systematic review and meta-analysis on HFNO concluded that this modality reduced the rate of intubation, mechanical ventilation and escalation for further respiratory support but comparison with NIV showed no better outcomes.[16]

Our study has its limitations. Firstly, the data collected was retrospectively from a single centre which could have an effect on the outcome and aetiology of ARF. Secondly, the management of patients was from a group of physicians. While the basic principles of management are consistent the finer aspects of treatment and decision to palliate or escalation of care could be variable. These could have had an effect on the final outcome for these patients. Furthermore, the time interval between the patient inclusions could have played a role especially due to the introduction of anti-fibrotics for the treatment of IPF and the use of HFNO in some patient groups which was introduced into the unit from mid-2014. We now know that anti-fibrotics in IPF do defer the time for acute exacerbations.[17]

V. Conclusion

In conclusion our findings suggest that patients with acute respiratory failure from ILD have a poor prognosis and NIV has a small but meaningful role. The outcome for patients with IPF needing enhanced respiratory support is poor with a very high mortality of 83%. Those patients surviving RHCU have a poor long term outcome with all patients not surviving at 3 months. This should make one consider the escalation plan for patients with IPF admitted with ARF prior to enhanced respiratory support. The principal predictor of outcome from our study is the ILD sub-type. While it's difficult to deduce the outcomes for the various ILD categories due to the heterogeneity of and small numbers in our study, it does highlight that early discussion about escalation of care is critical in these subsets of patients. The burden of additional co-morbidity cannot be ignored and can position additional challenges to the patient's physiological resolve and should be factored into decision-making regarding initiation of NIV and treatment escalation options for individual patients.

VI. Tables and Figures

Table 1: Demographics of study population

Baseline Characteristics	Deceased during admission to RHCU (n=36)	Survived from admission to RHCU (n=18)	p value
Demographics			
Male	21	14	
Female	15	4	
Age in years (range)	75 (48-85)	80.6 (62-87)	0.01*
Duration of diagnosis (months	18.7 ± 3.96	8.5 ± 9.36	0.47*

*P value of <0.05 is considered significant

Table 2: Admission lung functions, ABG values and blood counts between groups

	Deceased during admission to RHCU (n=36)	Survived from admission to RHCU (n=18)	p value
Lung function test			
FEV1 (% predicted)	72 ± 3.5	72 ± 3.6	0.25
FVC (% predicted)	65 ± 3.7	61 ± 4.6	0.20
FEV1/FVC (%)	87 ± 1.8	81 ± 2.6	0.049*
DLCO (% predicted)	40 ± 2.9	35 ± 3.3	0.30
Admission blood gases			
pH	7.39 ± 0.02	7.41 ± 0.03	0.17
PO2 (kPa)	7.32 ± 0.5	7.73 ± 0.72	0.29
PCO2 (kPa)	5.39 ± 0.39	5.99 ± 0.59	0.48
HCO3	23.7 ± 1.1	26.1 ± 1.1	0.15
Blood biochemistry on admission			
WCC	13.9 ± 0.9	13.2 ± 1.1	0.07
Neutrophils	11.6 ± 0.85	11.2 ± 0.9	0.06

Table 3: Associated comorbidities between groups

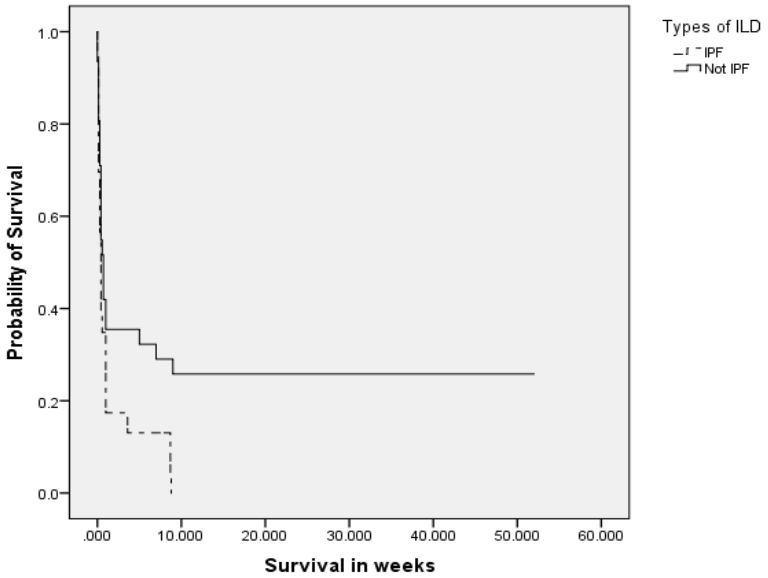
Respiratory comorbidities	Deceased during admission to RHCU (n=36)	Survived from admission to RHCU (n=18)
COPD	11%	22%
Pneumonia	44%	44%
COPD and Pneumonia	6%	17%
Long-term oxygen therapy	36%	44%
Non respiratory comorbidities		
Hypertension	19%	22%
Ischaemic heart disease	22%	11%
Pulmonary hypertension	6%	11%
Chronic kidney disease	8%	16%
Diabetes mellitus	14%	22%
Connective tissue disease	11%	16%
Gastro-intestinal	8%	6%

Table 4: ILD subtypes and outcome following admission to RHCU

ILD sub-type	Total n= 54	%	Death on RHCU	%	Survival from RHDU	%	Mortality at 30 days	%	Mortality at 3 months	%	Survival at one year	%
IPF	23	42.6	19	83	4	17	1	4	4	17	0	0
EAA	6	11.1	4	67	2	33	0	0	1	17	1	17
NSIP	6	11.1	4	67	2	33	1	17	1	17	1	17
RA-ILD and CTD-ILD	6	11.1	4	67	2	33	0	0	0	0	1	20
Sarcoidosis	3	5.6	1	33	2	67	1	33	2	67	0	0
Uncharacterised	3	5.6	1	33	2	67	0	0	0	0	2	67
Drug induced ILD	2	3.8	1	50	1	50	0	0	0	0	0	0
Others	5	9.5	2	40	3	60	1	20	1	20	1	20

Others [Asbestosis (n=1), CPFE, (n=2), PPFE (n=1)], uncharacterised ILD (n=3), sarcoidosis (n=3); CTD-ILD includes RA-ILD (n=5);

Figure 1: Kaplan-Meier survival based on the diagnosis of IPF or non IPF



Probability of survival in weeks following admission to the RHCU for patients with a diagnosis of IPF (broken lines) compared with the rest of ILD (non IPF) shown in solid lines.

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