Early hospital readmission increases short and long – term mortality in patients with interstitial lung disease.

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Abstract. Objective: To investigate the prognostic impact of early readmission (30 days) on hospitalized patients with Interstitial Lung Disease (ILD). **Methods:** Observational study analysing a cohort of patients hospitalized in a respiratory ward at a University Hospital. Demographic, clinical data and survival status were collected from patients' records. Early readmission was defined as hospitalization within 30 days after patient's discharge. The primary outcome was 90-day and 1-year all-cause mortality. **Results:** Between 2013 to 2016, a total of 2.238 patients were admitted to the respiratory ward and 98 (%) had a diagnosis of ILD. Among them, 74 patients were discharged (25% in-hospital mortality). Early readmission was observed in 15 cases (20.2%). Early readmitted patients were more frequently current smokers (20% vs. 2%, p=0.02). After a multivariate analysis, early readmission was found to be independently associated with 90-day and 1 year mortality (Odds Ratio (OR) 17.6, 95% Confidence Interval (CI) 4.5-69-2, p=0.001 and OR 4.5; 95CI 1.3-15.2, p=0.01, respectively). **Conclusion:** In patients with ILD, early readmission after hospitalization increases both short-term and long term mortality. Thus, preventing early readmission after discharge from hospital admission may have an impact in the clinical course of ILD patients. Further studies are required to identify factors contributing to early readmission.

Key words: Interstitial lung disease, Hospitalization, Mortality, Readmission.

Introduction

Interstitial lung disease (ILD) encompasses a group of rare lung disorders that share common clinical, radiological and pathological findings (1). The course of ILD is variable(2). Several disease progression markers have been identified, such as

age, lung function decline, extension of fibrotic features on lung imaging or underlying histology(3). Despite this, the disease behaviour remains highly unpredictable and more clinical tools to anticipate the evolution are needed.

Hospitalization has also been identified as a mortality risk factor in ILD. *Moua et al.* showed that in patients with fibrosing ILD, acute respiratory worsening leading to hospitalization were associated with significant in-hospital and post-discharge mortality(4). Although there are several factors linked to in-hospital mortality in ILD, such as clinical presentation, frailty, lung capacity or underlying disease, less is known about post-discharge mortality(5). In other chronic respiratory diseases, like Chronic Obstructive Pulmonary Disease (COPD), patients admitted with an exacerbation have an increased risk of future hospital readmissions(6,7), which is also related with a progressive increase in the risk of death(8). Nonetheless, COPD programs are focused on close follow-up after hospitalization(9,10). Hence, early readmission may influence the disease prognosis in ILD patients too, but to our knowledge, there are no previous studies evaluating this issue.

Therefore, the aim of this study was to investigate the impact of early readmission on mortality in a cohort of hospitalized patients with ILD.

Methods

Study design

Observational study conducted at the Respiratory Department of Hospital de la Santa Creu i Sant Pau, Barcelona. The study was approved by Hospital de la Santa Creu I Sant Pau ethics committee (IIBSP-EPI-2018-108).

The study was designed following STROBE recommendations for observational studies(11). Using electronic on-site records, we included all consecutive patients admitted to the respiratory ward of our institution from January 2013 to December 2016. Study data collection was anonymous. Regardless of the purpose of this study, patients were managed following institutional protocols based on national and international guidelines. Post-discharge one-year follow-up data was obtained either from our institutional clinical records or from a database of the health-care system in our region.

Primary outcome was 90-day and 1-year all-cause mortality after the index hospitalization. Secondary outcomes were: readmission, length of stay, reason for hospitalization and main diagnosis.

Study population

Of all patients hospitalized during this period in the Respiratory Department ward, we identified those with a diagnosis of ILD stated in their discharge letter in accordance with current *International Classification of Diseases, 10th Revision (ICD-10)* (12). ILD classification was defined by current international and national guidelines based on clinical, radiologic and histologic findings(13,14). Those not fulfilling current guidelines were not included. Patients that died during their first admission were excluded from analysis.

Variables

We collected the following data from patients' records:

Hospitalization: Demographic and clinical data, including comorbid conditions, treatments, history of smoking, laboratory tests and radiology results were assessed at the time of hospital admission.

Early readmission (30 days) after discharge.

ILD diagnosis was specifically reviewed in each case to avoid any potential bias. We collected data regarding diagnosis, including lung function tests, high resolution CT scans, laboratory tests and histology. We ensured that diagnosis was based on current guidelines.

Statistical analyses

Univariate statistics were used to test the association of demographic and clinical characteristics with early hospital readmission. Categorical variables are presented by frequencies and percentages; statistical differences were analysed using a $\chi 2$ test or a Fisher exact test when required. Continuous variables are presented as mean and SD or median and interquartile range (IQR) when data was not distributed normally. Statistical differences among continuous variables were analysed using a Student t test or the corresponding non-parametrical test when it was required. We performed logistic

regression analyses using clinical outcomes evaluated as dependent variables and early hospital readmission as an independent variable. We defined statistical significance as a 2-tailed p < 0.05. All analyses were performed with the SPSS 19.0 software program (SPSS Inc, Chicago, IL, USA).

Results

A total of 2.238 patients were admitted to the respiratory ward. Of them, 98 (4,4%) were hospitalized with a diagnosis of ILD. Finally, 74 patients were discharged (25% inpatient mortality). These patients were included in the study (Figure 1).

There were no missing cases during follow-up.

Main demographic and clinical findings are summarized in Table 1. Note that patients were old (median age 74±12), with a slight female predominance (55%) and were not smokers (54%). Chronic Hypersensitivity Pneumonitis and unclassifiable ILD were the most frequent diagnoses. The majority of patients had a high-resolution computed tomography (HRTC) inconsistent with usual interstitial pneumonia (UIP) patterns. Patients presented severe impairment in lung function.

Data regarding hospitalization is shown in Table 2. Mean length of admission was 8 ± 6.9 days, in the majority of cases due to a che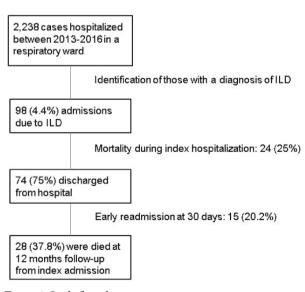st infection (63.5%). Acute respiratory failure was a common finding among these patients (92%) but only a minority required intubation and mechanical ventilation (4.1%) or high flow oxygen (4.1%). Bronchoscopy was performed in 20% of the cases.

A significant proportion of patients died during the 12 month follow-up period (28, 37.8%). Early readmission occurred in 15 cases (20.2%). No differences in clinical, laboratory and microbiological data were found among patients with or without early hospital readmission, except a higher rate of current smokers in the first group (20% vs. 2%, p=0.02) (table 3). Those patients with early readmission were also older (79 ± 6 vs 73 ± 13 years old) with a trend towards significance (p 0.07). Besides, the majority presented evidence of acute or sub-acute progression during the first admission (8/15). The causes of readmission were worsening of symptoms due to an acute or sub-acute progression of the disease (8/15), following by hospital acquired pneumonia (2/15), heart failure (2/15) and other extrapulmonary complications (3/15).

Regarding the main objective of this study, early hospital readmission (30 days) was associated with an increased risk of mortality at 90 days, 6 months and 1 year (Table 4). Early readmission was identified as an independent risk factor for 90-day mortality (Odds Ratio (OR) 17.6, 95% Confidence Interval (CI) 4.5-69-2, p=0.001), and 1-year mortality (OR 4.5 95CI 1.3-15.2, p=0.01 .

Discussion

Early hospital readmission (30th days) has been linked to an increased risk of mortality in several respiratory diseases. To our knowledge, this is the first study addressing the prognostic impact of early readmission in ILD patients. Our data shows that early readmission after an index hospitalization is independently associated with short- and long-term mortality in these patients, thus highlighting the importance of post-discharge care and the need for specific clinical care pathways in ILD.

Reducing early readmission of chronic diseases is an objective of many healthcare systems in developed countries, as these events have a significant impact on the course of the disease but many can be prevented(15). In COPD, it is well known that early readmission increases morbimortality(6,16). However, one in five patients with COPD that presented

Figure 1. Study flow chart.

Table 1. Demographic and clinical data summary.

Characteristic	N = 74
Age at admission, mean (range)	74 ± 12 (33 - 90)
Sex, M/F (%/%)	33/41 (45/55)

Smoker status, No. (%)
  Current smoker
  Ex - smoker
  Never smoker
	
	4 (5.4)
	30 (40.5)
	40 (54.1)

ILD-diagnoses, No. (%)
  Chronic HP
  Unclassifiable
  IPF
  CTD – ILD
  Drug / environmental
  OP
  Other ILD
	
	16 (21.6)
	13 (17.5)
	9 (12.1)
	9 (12.1)
	9 (12.1)
	8 (10.8)
	10 (13.5)

HRCT Patterns, No. (%)
  UIP Pattern
  Possible UIP Pattern
  Inconsistent with UIP Pattern
	
	10 (13.6)
	16 (21.6)
	48 (64.8)

PFT nearest to hospitalization	
FVC, % pred, mean ± SD	66.2 ± 21 (31 - 135) (n = 67)
FEV$_1$, % pred, mean ± SD	67.6 ± 21 (24 - 116) (n = 67)
TLC, % pred, mean ± SD	75.7 ± 21 (48 - 150) (n = 48)
D$_{LCO}$, % pred, mean ± SD	44.3 ± 19 (15 - 103) (n = 52)

Treatment, No. (%)
  None
  Immunosuppression
  Corticoid
	
	47 (63.5)
	11 (14.8)
	16 (29.7)

Oxygen Therapy, Yes/No (%/%)	27/47 (36.5/63.5)

Data are presented an *n (%)* unless otherwise indicated.
HP: Hypersensitivity pneumonitis; IPF: idiopathic pulmonary fibrosis; CTD-ILD: connective tissue disease-interstitial lung disease; OP: organizing pneumonia; HRCT: High-resolution computed tomography; UIP: usual interstitial pneumonia; PFT: pulmonary functional test; % pred: percent predicted.

with an acute exacerbation will require rehospitalization within 30 days of discharge after an admission[17]. It is estimated that around 10% to 55% of these episodes may be preventable as several factors have been identified as contributors of early readmission[17,18]. To tackle the problem, many countries have implemented programs to reduce COPD early readmissions[19]. Our study shows that in ILD, as in COPD, early readmission increases mortality. Thus, preventing early readmissions of these patients could have an impact on the course of the disease.

In our study, 24 patients died during the first hospitalization (25%). The course of ILD is variable,

but in fibrotic ILD-- especially Idiopathic Pulmonary Fibrosis (IPF)--there is a progressive loss of lung function disrupted by episodes of acute exacerbation (AE)[20]. These events usually require hospitalization and have a poor prognosis[21]. Patients with IPF and other ILD also require hospitalization related to other events (such as infection, cardiovascular or thromboembolic disease)[4]. However, in any case, hospitalization has a significant impact on the natural history of the disease[22]. *Durheim et al* reviewed the characteristics of 6.665 hospitalized patients with IPF identified from a representative US database[23]. Overall, in-patient mortality

Table 2. Hospitalization Characteristics

Characteristic	N = 74
Distribution of admission diagnoses, No. (%)	

Infection
  Acute exacerbation
  Sub-acute progression
  Heart failure
  Others
	47 (63.5)
	13 (17.6)
	7 (9.5)
	6 (8.1)
	1 (1.4)

Mean ± SD duration of hospitalization (range)	8 ± 6.9 (2 - 42)
Acute respiratory failure, No. (%)	68 (92)
Need for ICU admission, No. (%)	8 (10.8)
Intubation and mechanical ventilation, No. (%)	3 (4.1)
Need for nasal high flow oxygen, No. (%)	3 (4.1)
Bronchoscopy performed, No. (%)	15 (20.3)
High – dose IV steroids, No. (%)	3 (4.1)
Died within the first year after hospitalization, No. (%)	28 (37.8)

Data are presented an *n (%)* unless otherwise indicated.
ICU: Intensive care unit. IV: intravenous.

was 14.3%, and a total of 684 patients (10.3%) died during the first hospitalization. This percentage is close to a study conducted in Spain in 2014-2015 (14.94%)(24). In an acute setting, these numbers are exacerbated: *Moua et al.* analysed all consecutive patients with fibrotic ILD, hospitalized due to acute respiratory worsening in the institution from 2000 to 2014(4). Interestingly, in-hospital mortality during their first hospitalization accounts for 47% of IPF patients compared with 33% of patients without IPF. In-patient mortality in our study shifts between these studies because the nature of the hospitalization in our cohort includes both patients with AE and other causes of acute worsening, mainly chest infection.

Post discharge mortality, in our whole cohort, was 37.8 % at 12 months. There are few studies that have investigated the factors influencing post discharge mortality in ILD. In the study of *Moua T et al.* it was intriguing that post discharge survival was not related to the cause of hospitalization (AE versus no AE) in either IPF or non-IPF patients(4). More recently, *Yamazaki et al.* showed in a cohort of patients with chronic Idiopathic Interstitial Pneumonia that repeated hospitalization was associated with poor survival (25). But, interestingly, although survival rate after the first hospitalization was significantly better than those with multiple hospitalizations, there were no differences between the second

hospitalization and each subsequent. In our cohort, smoking was the only factor identified as a predictor of readmission. This is in accordance with data from COPD, which shows a smoke-free policy reduces rates of early readmission(26). Although it was not statistically significant, age seems to also have an impact on readmission. No other factors related to the lung condition were identified.

This study has limitations that need to be taken into account when interpreting the results. We recognize the possible bias due to its single-centre design and the retrospective nature itself. Conversely, the strength of our project is that the study analyses, for the first time, the risk factors for mortality associated with early readmission in ILD patients.

In conclusion, our study shows that in patients with ILD, early readmission (30 days) after a hospitalization increases mortality in the short (90 days) and long term (12 months). We found smoking as a possible contributor to early readmission but further research is needed to identify other risk factors. Implementing adequate post discharge programs in ILD to prevent early readmission may have an impact in the course of the disease.

Table 3. Predictors of readmission.

Variable	30th day Readmission N = 15	No 30th day Readmission N = 59	P Value
Age at admission, mean ±SD (range)	79 ± 6 (67 − 87)	73 ± 13 (33 − 90)	0.07
Sex M, No. (%)	9/15 (60)	24/59 (41)	0.25
Smoker Status (current) No. (%)	3/15 (20)	1/59 (2)	**0.026**
HRCT (UIP) No. (%)	7/15 (47)	19/59 (32)	0.37
Baseline PFR (% pred)			
FVC < 50%	2/13 (15)	16/54 (30)	0.5
D_{LCO} < 35%	3/9 (33)	20/43 (46)	0.7
Baseline treatment (immunosuppression) No. (%)	3/15 (20)	8/59 (14)	0.68
Baseline oxygen therapy, No. (%)	7/15 (47)	20/59 (34)	0.38
Admission type (infection), No. (%)	9/15 (60)	38/59 (64)	0.77
Duration of hospitalization (days), mean ±SD (range)	8 ± 3 (3 − 15)	8 ± 7 (2 − 42)	0.9
Acute respiratory failure, No. (%)	15/15 (100)	53/59 (90)	0.33
Need for mechanical ventilation, No. (%)	0/15 (0)	3/59 (5)	0.99
High − dose steroids	0/15 (0)	3/59	0.99

Data are presented an *n (%)* unless otherwise indicated.
HRCT: High-resolution computed tomography; UIP: usual interstitial pneumonia, PFT: pulmonary functional tests; % pred: percent predicted;

Table 4. Multivariate analysis of early hospital readmission (30 th day) as mortality risk factor.

Variable	Multivariable (OR, CI)	P Value
90 – days mortality	17.6 (4.5 − 69.2)	< 0.001
6 – months mortality	7.0 (2.0 − 24.3)	0.002
1 – year mortality	4.5 (1.3 − 15.2)	0.001

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