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# Utility of illness severity scores to predict mortality in patients hospitalised with respiratory deterioration of Idiopathic Pulmonary Fibrosis

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#### **Abstract**

*Introduction:* In the context of IPF, respiratory related admissions to hospital are associated with a high morbidity and short-term mortality with significant burden on secondary care services. It has yet to be determined how to accurately identify patients at risk of acute respiratory deterioration (ARD) or the prognosticating factors.

**Objective:** We sought to define the characteristics of hospitalised ARD-IPF patients in a real-world cohort and investigate factors associated with worse outcomes. Specifically, we wished to determine the association between baseline CURB-65 and NEWS2 and mortality in IPF, given illness severity scores have not previously been validated in this cohort.

*Methods:* Single-centre retrospective observational cohort study.

Results: Of 172 first hospitalisations for ARD, 27 admissions (15.7%) were due to an acute exacerbation of IPF (AE-IPF), 28 (16.3%) secondary to cardiac failure/fluid overload and 17 due to pneumonia (9.9%). Other admissions related to lower respiratory tract infection, extraparenchymal causes and those without a specific trigger. Baseline patient characteristics were comparable for all underlying aetiologies of ARD-IPF. Treatment pathways did not differ significantly between AE-IPF and other causes of ARD-IPF. Short term mortality was high, with approximately 22% patients dying within 30 days. Illness severity scores (NEWS-2 and CURB-65) were independent predictors of mortality in multivariable logistic regression modelling.

**Conclusions:** Our findings suggest significant mortality related to hospitalisation with ARD-IPF of any underlying cause. Our data supports the use of CURB-65 and NEWS-2 scores as illness severity scores that can provide a simple tool to help future prognostication in IPF. Research should be aimed at refining the management of these episodes, to try to reduce mortality, where possible, or to facilitate palliative care for those with adverse prognostic characteristics.

#### Introduction

Idiopathic pulmonary fibrosis (IPF) remains a rare but significant respiratory condition, defined by progressive lung fibrosis of unknown aetiology (1). Whilst some patients experience a steady decline in the their lung function over time, others experience sudden acute deteriorations that follow a period of relative stability (2). This heterogeneous disease course amongst individuals with IPF makes it challenging for healthcare professionals to predict the outcome of an individual patient, although the average life expectancy is only 3-5 years from diagnosis (3).

Collard *et al.* (4) recently published a conceptual framework for acute respiratory deteriorations (ARD) in IPF, subcategorising the aetiology of episodes as extra-parenchymal or parenchymal in origin. The presence of new diffuse pulmonary infiltrates on the background of established fibrosis, not fully explained by fluid overload or cardiac failure, describes an acute exacerbation of IPF (AE-IPF); a parenchymal cause of ARD-IPF whose definition has recently been revised to include episodes that may be 'triggered' by insults such as infection or those considered to be idiopathic in nature (4). It has been suggested that the prognosis of AE-IPF differs from other parenchymal causes of ARD-IPF (5); potentially highlighting the value of careful clinical phenotyping.

In the context of IPF, respiratory related admissions to hospital are associated with a high morbidity and short-term mortality with significant burden on secondary care services (6-8), although the factors that predict adverse outcomes in individuals are not fully understood. Early stratification of patients might be useful in planning referral for transplantation where applicable and/or advanced care planning discussions.

The CURB-65 score is an illness severity score, originally validated in pneumonia, enabling stratification of in-hospital mortality based on a 6-point score; one point for each of confusion, urea >7 mmol/l, respiratory rate (RR)  $\geq$ 30/min, low systolic (<90 mm Hg) or diastolic ( $\leq$ 60 mm Hg) blood pressure (BP), age  $\geq$ 65 years (9). It has subsequently been shown to predict inhospital mortality in exacerbations of Chronic Obstructive Pulmonary Disease (COPD) (10, 11). The National Early Warning Score (NEWS) is an alternative bedside tool incorporating seven objective measures of clinical status; RR, oxygen saturation, use of supplemental oxygen, temperature, systolic BP, heart rate, and consciousness level. It was originally developed to

rapidly identify in-hospital patients at risk of deterioration, and has subsequently been shown to predict in hospital mortality in older patients (12-15). To date, no study has assessed the prognostic value of these illness severity scores in predicting short term outcomes in ARD-IPF.

The aim of this study was to describe the characteristics of hospitalised ARD-IPF patients in a real-world cohort and investigate factors associated with worse outcomes. Specifically we sought to determine the association between CURB-65 and NEWS-2 baseline illness severity scores and mortality.

#### Methods

# Study design

This was a retrospective, single-centre observational cohort study undertaken at a large secondary care institution in the UK with specialist Interstitial Lung Disease (ILD) services available on site. The institution provides secondary and tertiary care to patients with interstitial lung disease with the South West of England supporting a local population of approximately 2 million. The study was approved by the Health Research Authority and health and Care Research Wales (HCRW), United Kingdom (IRAS 260771).

# Study Subjects

Consecutive patients admitted to the study centre with an ARD-IPF between January 2014 and December 2018 were included. Participants were identified retrospectively from hospital records using the International Classification of Diseases Tenth Revision (ICD-10) diagnostic code J84.1. As J-84.1 includes other fibrotic pulmonary diseases, validation of the clinical coding was performed on all patients in the cohort, cross-referencing the ICD code with written documentation of an ARD-IPF (i.e. patient was admitted with deteriorating respiratory function, under 1 month in duration, with a previous or concurrent diagnosis of IPF). All original diagnoses of IPF had been made by multidisciplinary team (MDT) consensus in accordance with 2011 ATS/ERS/JRS/ALAT guidelines (1). Throughout the process of data collection, the diagnosis of IPF was verified according to 2018 diagnostic criteria (3).

#### Outcome measures

Patients were categorised according to the conceptual framework as published by Collard *et al.* (4):

- 1. Extra-parenchymal causes were defined as pleural effusion, pneumothorax or pulmonary embolism.
- 2. AE-IPF was diagnosed according to the Collard (4) revised criteria: previous/concurrent IPF, worsening breathlessness <1 month duration, new bilateral ground-glass opacity and/or consolidation indicating widespread acute lung injury/diffuse alveolar damage, superimposed on a background pattern consistent with usual interstitial pneumonia (UIP) pattern on CT imaging, and deterioration not fully explained by cardiac failure or fluid overload. The definition of AE-IPF was broadened to include patients who had not had a CT Chest performed, but demonstrated new multilobar bilateral opacification on chest X-RAY, as interpreted by a Consultant Radiologist. AE-IPF was further sub-categorised into
  - a) triggered , defined as having a clear precipitant, for example infection, drugs or aspiration or
  - b) idiopathic.
- 3. Not-AE-IPF This included a group of patients with other parenchymal causes for their ARD-IPF, not attributed to an acute exacerbation:
  - a) Lower respiratory tract infection (LRTI), as a cause for ARD was defined in those patients with a normal CT and CXR but presence of C-reactive protein CRP >6mg/L.
  - b) Cardiac failure/fluid overload
  - c) Pneumonia
  - d) Disease progression
  - e) No specific trigger admission possibly related to anxiety or for symptomatic control and palliation
- 4. Unclassified ARD-IPF was used to refer to patients without CT Chest performed on admission and with a CXR that did not show any new changes compared to previous imaging, as interpreted by a consultant radiologist.

The primary outcome was mortality with a secondary outcome of overall length of stay. Independent variables were baseline illness severity scores, in the form of CURB-65 (9) and National Early Warning Score-2 (NEWS-2) (16). Data were collated on potential confounding factors, including demographics, seasonal influenza and pneumococcal (PneumoVax)

vaccination status and use of antifibrotic medications (for 6 months or more prior to admission). Gender-Age-Physiology (GAP) scores were calculated (17). The investigative and treatment pathway were recorded for each inpatient stay.

# Statistical analysis

Patient characteristics were tabulated based on the underlying aetiology of ARD-IPF as defined above. Categorical variables were presented as counts with percentages. All continuous data were non-parametric and therefore presented with medians and interquartile range (IQR). Differences between patient groups were evaluated using Mann Whitney U and Kruskal Wallis tests for continuous data and Fisher's exact test or Chi-squared testing for categorical data.

For the primary analysis, univariable and multivariable logistic regression analyses were performed to explore the relationship between baseline severity scores and mortality. The factors used in the multivariable model were decided *a priori* and included male gender, age, smoking status, GAP score, white cell count, neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP), CURB-65 and NEWS-2 score. Receiver operating characteristic curves were used to propose discriminating thresholds for variables of interest. For all tests a P < 0.05 was considered statistically significant. Data were analysed using Prism Version 8.0 (Graphpad software, San Diego, USA), with STATA (StataCorp, Texas, USA) for logistic regression analysis.

#### **Results**

#### Patient demographics

A total of 232 episodes of ARD-IPF were identified in 172 patients from January 2014 to December 2018. The majority of patients presenting with their first ARD-IPF were male (63% (n=108 of 172) and ex-smokers (56% (n=97)), with a median age of 77 years (IQR 70-85) (see *Table 1* and *Supplementary Table 1*). Patients had moderate restrictive disease with a median GAP score of 5, corresponding to GAP stage II.

Most patients had a known consensus diagnosis of IPF prior to admission (76.7%, n=132), with radiological pattern of definite usual interstitial pneumonia (UIP) in approximately half of all patients. Surgical lung biopsy had been rarely required to achieve the MDT consensus IPF diagnosis (n=15, 8.7%). In over 40% of first ARD-IPF presentations, the admission NEWS-2 score was  $\geq$ 5 and CURB-65 score  $\geq$ 2.

#### Underlying aetiology of ARD

**Figure 1**. depicts the underlying aetiology of first admissions with ARD-IPF (**Supplemental Table 1**. provides details of the underlying aetiology of all ARD-IPF admissions). Of the 172 first hospitalisations for ARD, nearly half (n=80, 46.5%) were due to parenchymal causes other than AE-IPF, specifically cardiac failure (n=28, 16.3%), pneumonia (n=17, 9.9%), disease progression (n=13, 7.6%) and lower respiratory tract infection (n=12, 7.0%). No specific trigger was identified in 10 patients (5.8%). These admissions were considered to be related to anxiety or for symptomatic control, with unchanged CT appearances and normal blood tests. Twenty-seven admissions (15.7%) were due to an acute exacerbation of IPF (AE-IPF), of which 26 were considered to be triggered events. Extra-parenchymal pathology was the cause of the ARD-IPF in 9 (5.2%) cases.

In approximately one third of patients (n=56, 32.6%), a CT scan was not performed as part of the admission and therefore it was felt that the cause for the ARD could not be fully characterised. All patients in this group had no new features reported on their CXR (by consultant radiologist). Of these, 55% (n=31) had a CRP  $\geq$  50mg/L and thus infection may have been a trigger.

# Clinical characteristics of ARD-IPF

The characteristics of patients admitted with an AE-IPF, as their first ARD-IPF, were compared to those presenting with other parenchymal causes and those with an uncharacterised ARD-IPF. Patients admitted with an AE-IPF were significantly younger than those admitted with other parenchymal causes for their respiratory deterioration (AE-IPF 75 years (IQR 66-80) vs parenchymal cause 81 years (IQR 71-86), but had comparable baseline CURB-65 and NEWS-2 scores, GAP stage, lung physiology and 6MWT parameters.

# Investigation of ARD-IPF

A potentially pathogenic organism was detected in 12.2% (n=21) of first ARD-IPF admissions (*Table 2*). Culture of sputum was the most common technique to detect a pathogen; accounting for 76.2% of all positive microbiological samples. Bronchoalveolar lavage (BAL) was rarely performed (n=6). The most commonly identified pathogen was *Pseudomonas aeruginosa* n=7, followed by *Moraxella catarrhalis* n=3.

Of those patients with a triggered AE-IPF, 4 patients had positive microbiological test results for *Pseudomonas aeruginosa, Haemophilus influenzae,* alpha haemolytic Streptococcus species and Cytomegalovirus *(Supplementary Table 2)*.

# Management of ARD-IPF

Three patients within the AE-IPF group, received invasive mechanical ventilation during their admission. All survived to hospital discharge; with a median length of stay of 20 days (IQR 14-42) and remained alive at 30 days post discharge (*Table 3*). No other patients presenting with ARD-IPF received IMV.

Antibiotics were used almost ubiquitously for patients admitted with a first episode of ARD-IPF (94.7%, n=163 of 172 first admissions), with a median duration of 10 days (IQR 7-14). There was no significant difference in the use of antibiotics for management of AE-IPF compared to with those with a parenchymal cause for ARD-IPF other than an AE.

Corticosteroids formed part of the treatment of 43% (n=74) of first admissions with ARD-IPF. Approximately one third of AE-IPF (n=9, 33.3%) and parenchymal ARD-IPF (n=25, 31.3%) received oral corticosteroids, whilst a minority (n=4 AE-IPF, n=11 other parenchymal causes) received methylprednisolone (standard regime 500-750mg methylprednisolone IV daily over 3 consecutive days).

# **Primary Outcome**

Short term mortality associated with first admissions with ARD-IPF was high; 17% of ARD-IPF admissions died as an inpatient, 22% within 30 days and 36% within 90 days of presentation (*Table 3*). There was no significant difference in the in-hospital, 30 day or 90 day mortality between uncharacterised, AE-IPF and parenchymal ARD-IPF.

Logistic regression analysis (*Table 4a and Table 4b*) was performed to assess risk factors associated with an independent increased risk of in-hospital and 90-day mortality of patients admitted with their first ARD-IPF and for all ARD-IPF patients. Baseline NEWS-2 and CURB-65 scores were predictive of in-hospital mortality for all ARD-IPF admissions (Odd's ratios: OR 4.06, P=<0.001; OR 4.08, P=0.007, respectively). Similarly, baseline NEWS-2, CURB-65 and GAP score were predictive of 90 day mortality in all ARD-IPF admissions (OR 1.74, P<0.001; OR 2.32, P=0.003; OR 1.58, P=0.023, respectively).

ROC curve analysis suggested that baseline CURB-65 and NEWS-2 gave the highest area under the curve (AUC) values for in-hospital mortality, 0.847 and 0.889 respectively (*Supplementary* 

**Figure 1**). Using the maximum Youden's index for each variable, baseline CURB-65 >3.5 and NEWS-2 score >6.5 were identified as the optimum cut-offs for predicting in-hospital mortality (**Table 5**).

# Secondary Outcomes

The median length of stay (LOS) for all patients admitted with their first ARD-IPF was 7 days (IQR 3-14). There was no significant difference in the LOS when comparing first admission with all admissions of ARD-IPF. In contrast, patients with an uncharacterised ARD-IPF had a significantly shorter LOS compared to those with a parenchymal cause of deterioration other than AE (median LOS uncharacterised 4 days (IQR 2-10) vs parenchymal 8 days (IQR 4-17) p=0.008), with no significant difference between AE-IPF and parenchymal ARD-IPF subgroups.

#### Discussion

In this single centre retrospective observational study, we examined the clinical characteristics of patients admitted with an ARD-IPF, at a UK hospital providing specialist ILD facilities. Our findings suggest there is significant mortality related to hospitalisations with ARD-IPF of any underlying cause. NEWS-2 and CURB-65 illness severity scores were independent predictors of mortality and may provide a simple tool to help future prognostication.

AE-IPF are known to be associated with high mortality and poor prognosis (18). Our data show that all ARD-IPF, not just AE-IPF, are associated with significant mortality. This finding is in concordance with Moua and colleagues (19), who demonstrated significant mortality associated with acute respiratory worsening (almost 80% at one year), irrespective of the underlying fibrotic lung disease or cause of respiratory decline. Our overall 90-day mortality rate for first ARD-IPF was comparable to that reported by other groups (5). In our cohort, there was no significant difference in mortality between AE-IPF and other parenchymal causes of ARD-IPF. This is in contrast to the findings of Teramachi *et al.* (5) who showed the 90-day mortality of AE-IPF patients was significantly higher compared to ARD of other parenchymal causes (46% (16/35) vs 17% (12/71) respectively; P = 0.002). These apparently conflicting findings may in part be explained by differences in study populations; an older population in our study and parenchymal causes of ARD-IPF included those with cardiac failure/fluid overload. Our findings also suggest that whilst clinicians should endeavour to make practical attempts at defining the cause for deterioration, clinicians/patients/families should understand the high mortality related to all causes respiratory worsening, including

those such as, pulmonary embolism or pneumonia/infection that may be considered as a potentially 'reversible cause' of breathlessness in an isolated context.

The identification of patients with poor prognosis from ARD-IPF remains a significant challenge for clinicians. Baseline FVC, TLCO, 6MWT parameters and even GAP-stage were not consistently independent predictors of outcome in this cohort, whilst increasing NEWS-2 and CURB-65 scores were independent predictors of both in-hospital and 90-day mortality for all ARD-IPF. Previous studies have reported several prognostic factors in patients with AE-IPF, including age, sex, symptom duration, smoking history, FVC and TLCO (20-22), but have not to our knowledge, investigated the role of these illness severity or early warning scores. We propose potential cut-offs for baseline CURB-65 and NEWS-2 scores through ROC curve and sensitivity analysis, although acknowledge that independent validation is required. If these finding are confirmed, then NEWS-2 and CURB-65 may prove simple and helpful tools in guiding prognostication of patients with ARD-IPF.

Post mortem samples (23, 24) and epidemiological data (25) both suggest that infection may be a triggering insult in some AE-IPF, although it remains unclear if a small number of specific pathogens are responsible for the majority of these cases and if there is a relationship between an identified pathogen and patient outcome. Our data shows that an infectious pathogen was identified in only a minority of patients admitted with ARD-IPF (12%) and as such, comparative analysis based on outcome could not be undertaken. The organisms isolated were predominantly gram-negative bacteria or 'cold-associated' viruses and in keeping with the findings of previous studies (26). One patient demonstrated CMV on BAL, associated with a positive viral PCR throat swab, but absence of peripheral blood antigenaemia, suggesting CMV colonisation rather than infection and supporting the assertion of latent infection and/or abnormal colonisation in the lungs of many IPF patients (26).

Antibiotics were used almost ubiquitously in cases of hospitalised ARD-IPF (94.7%), perhaps indicating that for clinicians, it is often impossible to exclude underlying infection as a potential contributor in these episodes. Almost half of all patients with AE-IPF, and 43% of ARD-IPF, received corticosteroids during their admission, although there is no clear evidence to support this approach. Current ATS/ERS IPF guidance makes a 'weak recommendation' for the use of corticosteroids in AE-IPF based on anecdotal reports of benefit in the context of

high mortality associated with these episodes (1). Thus, there remains a clear need for highquality controlled studies to support the evidence-based management of ARD-IPF.

Accurate definition of an AE-IPF was a significant challenge to this study, contributing to the small numbers reported and in part was related to missing data; CT Chest imaging was only performed in approximately 40% of first admissions with ARD-IPF, despite being recommended as part of the initial investigation to diagnose AE-IPF (4). Whilst this is in keeping with some of the available published studies (19, 27), it is considerably lower than that reported by Teramachi et al. in Japan (5). We suggest that combination of factors may explain these differences which may reflect the practice of initial treating non-ILD-specialists, patient preference and/or not practically possible or reasonable given the illness severity of the patient. That said, accurate definition of an AE-IPF is not unique challenge to our cohort; data from three IPFnet trials showed that 35% (31 of 88) of investigator-reported AE-IPF were subsequently categorised as unclassifiable because of missing data (28).

Other potential limitations of this relatively small observational study are acknowledged and include those intrinsic to retrospective studies, such as missing data and lack of appropriate controls. The identification of patients relied on a search of clinical coding databases and as such, the true incidence of ARD-IPF may not have been fully captured. This is a single centre experience and as such the findings might not be generalisable to other populations, particularly since this was an entirely Caucasian cohort. Whilst the study was a single centre study, the population described in this manuscript was heterogeneous in terms of aetiology of respiratory deterioration and a multicentre study may provide comparable data. Nonetheless, we are planning future multicentre validation and this initial single centre pilot work will provide valuable feasibility data to influence the scope and size of such work.

In conclusion, our findings suggest there is significant morbidity related to hospitalisation with ARD-IPF of any underlying cause, with both NEWS-2 and CURB-65 providing independent prediction of in-hospital and 90 day mortality. Further prospective work should be undertaken to verify these findings and refine the management of these episodes, particularly given the widespread use of antibiotics in this cohort. Given the significant 90-day post-hospitalisation mortality, if survival to discharge from ARD is achieved, early consideration for referral to transplantation where applicable and/or advanced care planning discussions is advised.

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**Figure 1: Aetiology of first admissions with acute respiratory deteriorations of Idiopathic Pulmonary Fibrosis (ARD-IPF).** ARD-IPF were subdivided according to the conceptual framework as published by Collard et al. (4). Abbreviations: AE-IPF, acute exacerbation of IPF; n, number; LRTI, Lower respiratory tract infection; CRP, C-reactive protein; CT, Computed Tomography of Chest.

Table 1. Characteristics of patients admitted with their first and all acute respiratory deterioration of idiopathic pulmonary fibrosis (ARD-IPF). Comparison of AE-IPF with those presenting with other parenchymal causes or an uncharacterised episode of ARD-IPF. There were no statistically significant differences between baseline characteristics of first and all admissions for ARD-IPF. Patients admitted with an AE-IPF were significantly younger than those admitted with other parenchymal causes for their respiratory deterioration (AE-IPF 75 years (IQR 66-80) vs parenchymal cause 81 years (IQR 71-86), but had comparable baseline NEWS-2 scores, GAP stage, lung physiology and 6MWT parameters. C-reactive protein was statistically higher in patients with AE-IPF than in patients with other parenchymal causes of ARD: 75mg/L (IQR 26-126) versus 34mg/L (IQR 12-73), respectively. Data presented as median and interquartile ranges (continuous data) or numbers and percentages (categorical). Continuous data analysed using Kruskal Wallis testing. Categorical data analysed using Chisquared testing. \*P<0.05 was considered statistically significant.

Abbreviations: NEWS-2, National Early Warning Score 2; WBC, White blood count; NLR, neutrophil: lymphocyte ratio; CRP, C-reactive protein; IQR, interquartile range; AE, acute

exacerbation; P, parenchymal; GAP, gender, age, physiology; n, number; %, percentage; FVC, Forced vital capacity; TLCO, transfer factor for carbon monoxide; UIP, usual interstitial pneumonia.

Table 2: Microbiological investigations undertaken for first admissions with acute respiratory deteriorations of idiopathic pulmonary fibrosis (ARD-IPF). Abbreviations: n, number; %, percentage; MC&S, microscopy, culture and sensitvity; UAT, urinary antigen testing; PCR, polymerase chain reaction. \* Sputum culture identified Coliforms (2), Haemophillus influenzae (1), Moraxella catarrhalis (3), Pseudomonas aeruginosa (7), Raoutella plantiola (1), Serratia marcescans (1) and Streptococcus pneumoniae (1). \*\* Blood culture revealed Pseudomonas aeruginosa infection. # Oropharyngeal viral PCR revealed Cytomegalovirus (CMV) (1), Influenza A (1), Rhinovirus (2) and Respiratory Syncytial Virus (1). † Bronchoalveolar lavage identified CMV (1), alpha haemolytic streptococcus (1) and Pseudomonas aeruginosa (1). One patient was identified with pseudomonas both in sputum and blood cultures. One patient had both rhinovirus positivity on viral PCR and streptococcus pneumoniae in sputum culture.

Table 3. Outcomes of patients admitted with their first and all acute respiratory deterioration of idiopathic pulmonary fibrosis (ARD-IPF). Comparison of AE-IPF with those presenting with other parenchymal causes or an uncharacterised episode of ARD-IPF. There was no statistical difference in the length of antibiotics, use of corticosteroids, level of respiratory support or mortality between groups. Patients with an uncharacterised ARD-IPF had a significantly shorter LOS compared to those with a parenchymal cause of deterioration other than AE (median LOS uncharacterised 4 days (IQR 2-10) vs parenchymal 8 days (IQR 4-17) p=0.008. Data presented as median and interquartile ranges (continuous data) or numbers and percentages (categorical). Continuous data analysed using Kruskal Wallis testing. Categorical data analysed using Chi-squared testing. \*P<0.05 was considered statistically significant. Abbreviations: n, number; IV, intravenous; IQR, interquartile range. LOS, length of stay; AE, acute exacerbation; U, uncharacterised; P, parenchymal; HFNO, high flow nasal oxygen, NIV, non-invasive ventilation, IMV, invasive mechanical ventilation, %, percentage.

Table 4: Association of baseline patient factors with a) in-hospital mortality (top) b) 90-day mortality (below) following first admission and all admissions with ARD-IPF. Odds ratios (OR) were calculated and logistic regression analyses performed to identify factors

independently predicting mortality. Baseline NEWS-2 and CURB-65 scores were predictive of in-hospital mortality for all ARD-IPF admissions (OR 4.06, p=<0.001; OR 4.08, p=0.007, respectively). Similarly, baseline NEWS-2, CURB-65 and GAP score were predictive of 90 day mortality in all ARD-IPF admissions (OR 1.74, <0.001; 2.32, 0.003; 1.58, 0.023, respectively). In this cohort, male gender was associated with increased survival of all ARD-IPF patients as in-patients and also at 90-days for those with a first admission of ARD-IPF (- OR 0.07; p= 0.019 and OR 0.1; p=0.031, respectively).

Table 5: Outcomes of receiver operating characteristic (ROC) curve analysis for determining the optimal cut-off values for CURB-65 and NEWS-2 scores, correlating with in-hospital or 90-day mortality in all acute respiratory deteriorations of Idiopathic Pulmonary fibrosis (ARD-IPF). ROC curve analysis suggested that baseline CURB-65 and NEWS-2 gave the highest area under the curve (AUC) values for in-hospital mortality, 0.847 and 0.889 respectively Abbreviations: AUC, Area under the curve; CI, confidence interval; P, significance value; % percentage.

Supplementary Table 1: Additional baseline demographics of patients admitted with their first acute respiratory deterioration of idiopathic pulmonary fibrosis (ARD-IPF). Abbreviations: IQR, interquartile range; n, number; FVC, Forced vital capacity; TLCO, transfer factor for carbon monoxide; GAP, gender-age-physiology; MDT, multidisciplinary team; UIP, usual interstitial pneumonia; %, percentage.

Supplementary Table 2: Microbiological test results in patients presenting with AE-IPF, parenchymal or un-characterised ARD. ^^ Pseudomonas aeruginosa (1), Haemophilus influenzae (1). \* Both sputum and blood cultures grew the same organism, Pseudomonas aeruginosa. + One patient had co-infection with rhinovirus and Streptococcus pneumoniae. ^ Alpha haemolytic Streptococcus species and Cytomegalovirus infection. ++ same organism identified in sputum and on BAL, Pseudomonas aeruginosa. Abbreviations: n, number; CRP, C-reactive protein; PCR, Polymerase chain reaction; BAL, bronchoalveolar lavage.

**Supplementary Figure 1:** Receiver operating characteristics (ROC) curve analysis of baseline CURB-65 and NEWS-2 scores for in-hospital and 90-day mortality following admission for an acute respiratory deterioration of Idiopathic Pulmonary Fibrosis. CURB-65 and NEWS-2 for inhospital mortality had the highest area under the curve, 0.8473 and 0.8891 respectively.

#### **Author statement:**

SLB provided conceptualisation of the project. CH and DH collected the data. AB provided support with statistical analysis. SLB and CH wrote the first draft. AB and HA reviewed the final manuscript.

Conflicts of Interest: SLB and HA have received honoraria from Boehringer Ingelheim. CH, AB and DH have no conflicts of interest to declare.

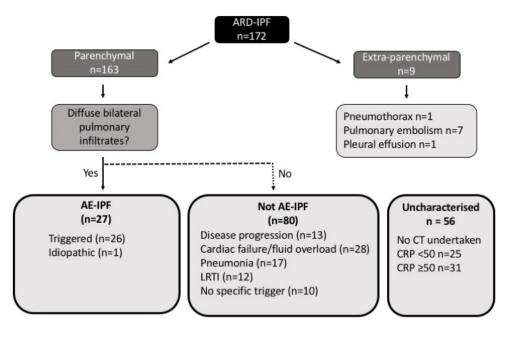


Figure 1.

Figure 1: Aetiology of first admissions with acute respiratory deteriorations of Idiopathic Pulmonary Fibrosis (ARD-IPF). ARD-IPF were subdivided according to the conceptual framework as published by Collard et al. (4). Abbreviations: AE-IPF, acute exacerbation of IPF; n, number; LRTI, Lower respiratory tract infection; CRP, C-reactive protein; CT, Computed Tomography of Chest.

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Characteristic	First Admission (n=172)	All ARD-IPF (n=232)	P value	Uncharacterised (n=56)	AE-IPF (n=27)	Other Parenchymal cause (n=80)	P value	
Age (median, IQR)	77 (70-85)	-	-	77 (71-85)	75 (66-80)	81 (71-86)	0.035* AE vs P	
Gender, males, n (%)	108 (62.8)	-	-	31 (55.4)	21 (77.8)	51 (63.8)	0.208	
Total GAP score (median, IQR)	5 (4-6), n=116	-	-	5 (3-6), n=39	5 (4-6), n=19	4.5 (4-5), n=52	0.810	
Baseline lung function (median, IQR)								
FVC % predicted	70 (52-85), n=123	-	-	74 (53-89), n=40	70 (51-80), n=19	67 (52-86), n=53	0.467	
TLCO % predicted	38 (30-48), n=119	-	-	30 (30-51), n=39	36 (26-46), n=19	38 (29-50), n=53	0.683	
6-minute walk test (6MWT)								
(median, IQR)								
6MWT distance (m)	280 (200-330), n=119	-	-	290 (200-335), n=41	260 (140-320), n=19	270 (200-320), n=52	0.535	
6MWT minimum sats (%)	86 (83-88), n=110	-	-	86 (83-89), n=41	85 (83-91), n=19	86 (80-88), n=60	0.447	
CURB-65 Score, n (%)								
0-1	32 (18.6)	40 (17.2)	0.923	13 (23.2)	7 (25.9)	11 (13.8)	0.550	
2	70 (40.7)	94 (40.5)		23 (41.1)	10 (37.0)	35 (43.8)		
≥ 3	70 (40.7)	98 (42.2)		20 (35.7)	10 (37.0)	34 42.5)		
NEWS-2 Score, n (%)								
0	0 (0)	0 (0)	0.991	0 (0)	0 (0)	0 (0)	>0.999	
1-4	93 (54.1)	125 (53.9)		31 (55.4)	15 (55.6)	31 (38.8)		
5-6	48 (27.9)	66 (28.4)		17 (30.4)	8 (29.6)	17 (21.3)		
≥7	31 (18.0)	41 (17.6)		8 (14.3)	4 (14.8)	8 (10.0)		
Blood tests								
WBC (median, IQR)	10.9 (8.1-13.8)	11.2 (8.6-14.7)	0.196	11.7 (8.8-15.2)	9.6 (7.8-12.8)	10.4 (7.7-13.2)	0.209	
NLR (median, IQR)	1.28 (1.16-1.48)	1.27 (1.16-1.44)	0.580	1.2 (1.2-1.4)	1.3 (1.1-1.4)	1.3 (1.2-1.5)	0.458	
CRP (median, IQR)	47 (17-85)	53 (19.3-98.3)	0.358	53 (21-81)	75 (26-126)	34 (12-73)	0.014* AE vs P	

Table 1. Characteristics of patients admitted with their first and all acute respiratory deterioration of idiopathic pulmonary fibrosis (ARD-IPF). Comparison of AE-IPF with those presenting with other parenchymal causes or an uncharacterised episode of ARD-IPF. There were no statistically significant differences between baseline characteristics of first and all admissions for ARD-IPF. Patients admitted with an AE-IPF were significantly younger than those admitted with

other parenchymal causes for their respiratory deterioration (AE-IPF 75 years (IQR 66-80) vs parenchymal cause 81 years (IQR 71-86), but had comparable baseline NEWS-2 scores, GAP stage, lung physiology and 6MWT parameters. C-reactive protein was statistically higher in patients with AE-IPF than in patients with other parenchymal causes of ARD: 75mg/L (IQR 26-126) versus 34mg/L (IQR 12-73), respectively. Data presented as median and interquartile ranges (continuous data) or numbers and percentages (categorical). Continuous data analysed using Kruskal Wallis testing. Categorical data analysed using Chi-squared testing. \*P<0.05 was considered statistically significant.

Abbreviations: NEWS-2, National Early Warning Score 2; WBC, White blood count; NLR, neutrophil: lymphocyte ratio; CRP, C-reactive protein; IQR, interquartile range; AE, acute exacerbation; P, parenchymal; GAP, gender, age, physiology; n, number; %, percentage; FVC, Forced vital capacity; TLCO, transfer factor for carbon monoxide; UIP, usual interstitial pneumonia.

Microbiological Test, n (%)	First Admission
	(Total n=172)
	Data presented as n, (%)
No pathogen identified	151 (87.8)
Pathogen identified	21 (12.2)
Sputum MC&S	
Not performed/rejected	95 (55.2)
Negative culture	52 (30.2)
Non-specific culture	9 (5.2)
Positive culture *	16 (9.3)
Blood Culture	
Not performed	80 (46.5)
Negative culture	91 (52.9)
Positive culture **	1 (0.6)
Pneumococcal UAT	
Not performed	128 (74.4)
Negative result	44 (25.6)
Oropharyngeal viral PCR	
Not performed	144 (83.7)
Negative result	23 (13.4)
Positive result #	5 (2.9)
Other positive microbiological tests	
Atypical pneumonia serology	1
Bronchoalveolar lavage †	3

Table 2: Microbiological investigations undertaken for first admissions with acute respiratory deteriorations of idiopathic pulmonary fibrosis (ARD-IPF). Abbreviations: n, number; %, percentage; MC&S, microscopy, culture and sensitvity; UAT, urinary antigen testing; PCR, polymerase chain reaction. \* Sputum culture identified Coliforms (2), Haemophillus influenzae (1), Moraxella catarrhalis (3), Pseudomonas aeruginosa (7), Raoutella plantiola (1), Serratia marcescans (1) and Streptococcus pneumoniae (1). \*\* Blood culture revealed Pseudomonas aeruginosa infection. # Oropharyngeal viral PCR revealed Cytomegalovirus (CMV) (1), Influenza A (1), Rhinovirus (2) and Respiratory Syncytial Virus (1). † Bronchoalveolar lavage identified CMV (1), alpha haemolytic streptococcus (1) and

*Pseudomonas aeruginosa* (1). One patient was identified with pseudomonas both in sputum and blood cultures. One patient had both rhinovirus positivity on viral PCR and streptococcus pneumoniae in sputum culture.

Outcome	First Admission (n=172)	All ARD-IPF (n=232)	P value	Uncharacterised (n=56)	AE-IPF (n=27)	Other Parenchymal cause (n=80)	P value
Respiratory support, n (%)							
None	11 (6.4)	14 (6.0)	0.958	3 (5.4)	1 (3.7)	6 (7.5)	0.082
Oxygen	66 (38.4)	86 (37.1)		27 (48.2)	8 (29.6)	23 (28.8)	
HFNO	49 (28.5)	72 (31.0)		10 (17.9)	12 (44.4)	27 (33.8)	
NIV	43 (25.0)	55 (23.7)		16 (28.6)	3 (11.1)	24 (30.0)	
IMV	3 (1.7)	5 (2.2)		0 (0)	3 (11.1)	0 (0)	
Treatment	160 (0.1 =)	247 (22 7)		<b>-</b> . (0.5. 1)	20 (100 0)	<b></b> (00.0)	,
Received antibiotics (> 2 days), n (%)	163 (94.7)	217 (93.7)	0.674	54 (96.4)	20 (100.0)	75 (93.8)	n/s
Duration antibiotic course, days, (median, IQR)	10 (7-14)	10 (7-14)	0.869	7 (5-14)	10 (7-14)	10 (7-14)	0.347
Received corticosteroids, n (%)	74 (43.0)	98 (42.2)	0.919	34 (60.7)	14 (51.9)	44 (55)	0.700
Oral corticosteroids, n (%)	51 (29.7)	68 (29.3)	>0.99	16 (28.6)	9 (33.3)	25 (31.3)	
IV corticosteroids, n (%)	23 (13.4)	30 (12.9)	>0.99	6 (10.7)	4 (14.8)	11 (13.8)	
Hospital length of stay, days,							
(median, IQR)	7 (3-14)	7 (3-14)	0.901	4 (2-10)	9 (4-17)	8 (4-17)	0.008* U vs P
Mortality, n (%)							
Inpatient mortality	30 (17.2)	40 (17.2)	>0.99	9 (16.1)	2 (7.4)	16 (20.0)	0.312
30-day mortality	39 (22.4)	53 (22.8)	>0.99	13 (23.2)	6 (22.2)	17 (21.3)	0.942
90-day mortality	62 (35.6)	85 (36.6)	0.917	18 (32.1)	10 (37.0)	27 (33.8)	0.784

Table 3. Outcomes of patients admitted with their first and all acute respiratory deterioration of idiopathic pulmonary fibrosis (ARD-IPF). Comparison of AE-IPF with those presenting with other parenchymal causes or an uncharacterised episode of ARD-IPF. There was no statistical difference in the length of antibiotics, use of corticosteroids, level of respiratory support or mortality between groups. Patients with an uncharacterised ARD-IPF had a significantly shorter LOS compared to those with a parenchymal cause of deterioration other than AE (median LOS uncharacterised 4 days (IQR 2-10) vs parenchymal 8 days (IQR 4-17) p=0.008.

Data presented as median and interquartile ranges (continuous data) or numbers and percentages (categorical). Continuous data analysed using Kruskal Wallis testing. Categorical data analysed using Chi-squared testing. \*P<0.05 was considered statistically significant.

Abbreviations: n, number; IV, intravenous; IQR, interquartile range. LOS, length of stay; AE, acute exacerbation; U, uncharacterised; P, parenchymal; HFNO, high flow nasal oxygen, NIV, non-invasive ventilation, IMV, invasive mechanical ventilation, %, percentage.

a)

	First admission with	h ARD-IPF	All ARD-IPF		
Variable	Odds Ratio (C.I.)	P value	Odds Ratio (C.I.)	P value	
Male	0.03 (0.00-9.18)	0.227	0.07 (0.01-0.65)	0.019	
Age	1.15 (0.94-1.41)	0.175	1.02 (0.94-1.11)	0.564	
Smoking status	0.40 (0.01-24.7)	0.665	1.65 (0.38-7.15)	0.501	
GAP	0.45 (0.69-2.98)	0.409	1.04 (0.56-1.91)	0.912	
WCC	0.79 (0.48-1.31)	0.363	0.90 (0.75-1.08)	0.260	
NLR	0.95 (0.80-1.13)	0.559	1.04 (0.92-1.18)	0.528	
CRP	1.02 (0.98-1.05)	0.376	1.01 (1.00-1.01)	0.171	
NEWS-2	6.68 (1.42-31.3)	0.016	4.06 (2.23-7.41)	<0.001	
CURB-65	10.03 (0.24-420.8)	0.227	4.08 (1.47-11.31)	0.007	

b)

	First admission wit	th ARD-IPF	All ARD-IPF		
Variable	Odds Ratio (C.I.)	P value	Odds Ratio (C.I.)	P value	
Male	0.10 (0.01-0.82)	0.031	0.36 (0.11-1.15)	0.084	
Age	1.02 (0.95-1.10)	0.506	1.01 (0.96-1.05)	0.770	
Smoking status	1.16 (0.23-5.81)	0.854	1.34 (0.58-3.08)	0.494	
GAP	2.51 (1.16-5.41)	0.019	1.58 (1.06-2.34)	0.023	
WCC	1.12 (0.92-1.37)	0.267	1.02 (0.92-1.12)	0.735	
NLR	1.00 (0.94-1.06)	0.931	0.98 (0.94-1.03)	0.498	
CRP	1.00 (1.00-1.01)	0.518	1.00 (1.00-1.01)	0.074	
NEWS-2	1.40 (0.99-2.03)	0.074	1.74 (1.37-2.21)	<0.001	
CURB-65	1.53 (0.59-3.98)	0.386	2.32 (1.33-4.03)	0.003	

Table 4: Association of baseline patient factors with a) in-hospital mortality (top) b) 90-day mortality (below) following first admission and all admissions with ARD-IPF. Odds ratios (OR) were calculated and logistic regression analyses performed to identify factors independently predicting mortality. Baseline NEWS-2 and CURB-65 scores were predictive of in-hospital mortality for all ARD-IPF admissions (OR 4.06, p=<0.001; OR 4.08, p=0.007, respectively). Similarly, baseline NEWS-2, CURB-65 and GAP score were predictive of 90 day mortality in all ARD-IPF admissions (OR 1.74, <0.001; 2.32, 0.003; 1.58, 0.023, respectively). In this cohort, male gender was associated with

increased survival of all ARD-IPF patients as in-patients and also at 90-days for those with a first admission of ARD-IPF (- OR 0.07; p=0.019 and OR 0.1; p=0.031, respectively).

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	AUC	95% CI	P value	Decision	Sensitivity	Specificity	Youden's
				point	%	%	Index (J)
CURB-65 in	0.847	0.774 to 0.920	<0.0001	>3.5	94.8	67.5	0.62
hospital mortality							
CURB-65	0.763	0.696 to 0.830	<0.0001	>3.5	98.6	41.2	0.40
90 day mortality							
NEWS-2 in-hospital	0.889	0.820 to 0.958	<0.0001	>6.5	94.3	75.0	0.69
mortality							Δ <u>α</u>
NEWS-2	0.744	0.674 to 0.815	<0.0001	>5.5	86.4	55.3	0.42
90 day mortality							3 3

Table 5: Outcomes of receiver operating characteristic (ROC) curve analysis for determining the optimal cut-off values for CURB-65 and NEWS-2 scores, correlating with in-hospital or 90-day mortality in all acute respiratory deteriorations of Idiopathic Pulmonary fibrosis (ARD-IPF). ROC curve analysis suggested that baseline CURB-65 and NEWS-2 gave the highest area under the curve (AUC) values for in-hospital mortality, 0.847 and 0.889 respectively. Abbreviations: AUC, Area under the curve; CI, confidence interval; P, significance value; % percentage.