

Outcome of Hospitalization for COVID-19 in Patients with Interstitial Lung Disease: An International Multicenter Study

Thomas M Drake¹, Annemarie B Docherty¹, Ewen M Harrison¹, Jennifer K Quint², Huzaifa Adamali^{3,4}, Sarah Agnew⁵, Suresh Babu⁶, Christopher M Barber⁷, Shaney Barratt^{3,4}, Elisabeth Bendstrup⁸, Stephen Bianchi⁷, Diego Castillo Villegas⁹, Nazia Chaudhuri^{10,11}, Felix Chua¹², Robina Coker¹³, William Chang¹⁴, Anjali Cranshaw¹⁵, Louise E. Crowley¹⁶, Davinder Dosanjh¹⁵, Christine A Fiddler¹⁷, Ian A. Forrest¹⁸, Peter M George^{2,12}, Michael A Gibbons¹⁹, Katherine Groom¹³, Sarah Haney²⁰, Simon P Hart²¹, Emily Heiden²², Michael Henry²⁴, Ling-Pei Ho²⁵, Rachel K Hoyles²⁵, John Hutchinson²⁶, Killian Hurley^{27,28}, Mark Jones^{22,23}, Steve Jones²⁹, Maria Kokosi^{12,40}, Michael Kreuter³⁰, Laura S MacKay²⁰, Siva Mahendran³¹, George Margaritopoulos¹⁰, Maria Molina-Molina³², Philip L Molyneaux², Aiden O'Brien³³, Katherine O'Reilly³⁴, Alice Packham¹⁵, Helen Parfrey¹⁷, Venerino Poletti^{8,35}, Joanna C. Porter³⁶, Elisabetta Renzoni¹², Pilar Rivera-Ortega¹⁰, Anne-Marie Russell^{2,41}, Gauri Saini¹⁴, Lisa G Spencer⁵, Giulia M. Stella³⁷, Helen Stone³⁸, Sharon Sturney³⁹, David Thickett^{15,16}, Muhunthan Thillai¹⁷, Tim Wallis^{22,23}, Katie Ward², Athol U Wells¹², Alex West⁴⁰, Melissa Wickremasinghe⁴¹, Felix Woodhead⁴², Glenn Hearson⁴³, Lucy Howard⁴³, J Kenneth Baillie⁴⁴, Peter J.M. Openshaw², Malcolm G Semple⁴⁵, Iain Stewart⁴³, ISARIC4C Investigators, R Gisli Jenkins^{14,43}

1 Centre for Medical Informatics, The Usher Institute, University of Edinburgh, Edinburgh, EH16 4UX

2 National Heart and Lung Institute, Imperial College, London, UK

3 Bristol Interstitial Lung Disease Service, North Bristol NHS Trust, Southmead Hospital, Bristol, UK, BS10 5NB.

- 4 Academic Respiratory Unit, University of Bristol, Southmead Hospital, Bristol, BS10 5NB.
- 5 Liverpool Interstitial Lung Disease Service, Aintree site, Liverpool University Hospitals NHS Foundation Trust, Liverpool, L9 7AL, UK.
- 6 Queen Alexandra Hospital, Portsmouth, UK.
- 7 Northern General Hospital, Sheffield, S5 7AU, UK.
- 8 Centre for Rare Lung Diseases, Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark
- 9 ILD Unit, Respiratory Medicine Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.
- 10 ILD Unit, Manchester University Hospital NHS FT, Wythenshawe Hospital, Southmoor Road, Wythenshawe, Manchester M23 9LT, UK
- 11 University of Manchester, Manchester, UK
- 12 Royal Brompton and Harefield NHS Foundation Trust, London, UK
- 13 Respiratory Medicine, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London W12 0HS, UK
- 14 Nottingham University Hospitals NHS Trust, City Campus, Nottingham, NG5 1PB, UK
- 15 Birmingham Interstitial Lung Disease Unit, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.
- 16 University of Birmingham, Birmingham, UK.
- 17 Cambridge Interstitial Lung Disease Service, Royal Papworth Hospital NHS Foundation Trust, Cambridge Biomedical Campus, Cambridge CB2 0AY, UK
- 18 Department of Respiratory Medicine, Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, NE1 4LP, UK.
- 19 South West Peninsula ILD Network, Royal Devon & Exeter Foundation NHS Trust

Barrack Road, Exeter EX2 5DW, UK

20 Northumbria Specialist Emergency Care Hospital, Northumbria Way, Northumbria

Healthcare NHS Foundation Trust, Cramlington, NE23 6NZ

21 Respiratory Research Group, Hull York Medical School, Castle Hill Hospital, Cottingham,

UK, HU16 5JQ

22 University Hospitals Southampton NHS Foundation Trust, Southampton, UK

23 NIHR Southampton Biomedical Research Centre & Clinical and Experimental Sciences,

University of Southampton, Southampton, UK

24 Cork University Hospital, Cork, Ireland

25 Oxford Interstitial Lung Disease Service, Oxford University Hospitals NHS Foundation

Trust, Oxford, OX3 7LE, UK

26 King's Mill Hospital, Sutton-in-Ashfield, Nottinghamshire, NG17 4JL, UK

27 Department of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland.

28 Beaumont Hospital, Dublin, Ireland.

29 Action for Pulmonary Fibrosis, Stuart House, Peterborough, PE1 5DD, UK.

30 Center for interstitial and rare lung diseases, Pneumology, Thoraxklinik, University of

Heidelberg, Germany and German Center for Lung Research, 69126 Heidelberg, Germany

31 Kingston Hospital NHS Foundation Trust. Galsworthy Road, Kingston upon Thames,

Surrey KT2 7QB, UK.

32 ILD Unit, Respiratory Department, University Hospital of Bellvitge, IDIBELL, Hospitalet de

Llobregat, Barcelona, Spain.

33 University Hospital Limerick, Dooradoyle, Limerick, Ireland.

34 Department of Respiratory Medicine, Mater Misericordiae University Hospital, Dublin,

Ireland.

35 Department of Diseases of the Thorax, Morgagni Hospital, Forli, Italy.

36 UCL Respiratory, University College London and ILD Service, University College London Hospitals NHS Foundation Trust, London, UK.

37 Laboratory of Biochemistry and Genetics, Pneumology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

38 University Hospital North Midlands NHS Trust, Royal Stoke University Hospital, Newcastle Road, Stoke-on-Trent, ST4 6QG, UK.

39 Royal United Hospitals Bath NHS Foundation Trust, Combe Park, Bath BA1 3NG, UK

40 Guys & St Thomas' NHS Trust, Westminster Bridge Road, London, SE1 7EH, UK

41 Imperial Healthcare NHS Trust, St Mary's Hospital, The Bays, S Wharf Rd, Paddington, London W2 1NY, UK.

42 Institute of Lung Health, Interstitial Lung Disease Unit, Glenfield Hospital, Leicester, LE3 9QP, UK.

43 NIHR Biomedical Research Centre, Respiratory Research Unit, University of Nottingham, Nottingham NG5 1PB, UK

44 Roslin Institute, University of Edinburgh, Edinburgh, UK and Intensive Care Unit, Royal Infirmary Edinburgh, Edinburgh, UK.

45 NIHR Health Protection Research Unit in Emerging and Zoonotic Infections, Institute of Infection, Veterinary and Ecological Sciences, Faculty of Health and Life Sciences, University of Liverpool, Liverpool, UK and Respiratory Medicine, Alder Hey Children's Hospital, Liverpool L12 2AP, UK

Running title: COVID-19 and interstitial lung disease

Correspondence to:

Professor R Gisli Jenkins, MD, PhD

NIHR Research Professor and Professor of Experimental Medicine

NIHR BRC Nottingham Respiratory Research Unit

University of Nottingham

Hucknall Road

Nottingham

UK NG14 7FW

Telephone: +44 115 823 1711

E-mail: gisli.jenkins@nottingham.ac.uk

Author contributions: RGJ designed and conceived the study and drafted the manuscript.

TMD analyzed the data and drafted the manuscript. ABD, EMH, JKQ, IS developed the

analysis plan and analyzed the data and revised the manuscript. LH, GH collated and curated

all data and revised the manuscript. HA, SA, SB, CMB, SB, EB, SB, DCV, NC, FC, RC, WC, AC,

LEC, DD, CAF, IAF, PG, MAG, KG, SH, SPH, EH, MH, LPH, RKH, JH, KH, MJ, MK, MK, LM, SV,

GM, MMM, PLM, AOB, KOR, AP, HP, VP, JP, ER, PRO, AMR, GS, LGS, GMS, HS, SS, DT, MT,

TW, KW, AUW, AW, MW, FW, JKB, PJMO, MGS helped design the study, contributed data

and revised the manuscript for important intellectual content. SJ helped design study and

revised the manuscript for important intellectual content. All authors have provided final

approval of the version submitted for publication; and agreement to be accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any

part of the work are appropriately investigated and resolved.

Subject descriptor: 9.23 Interstitial Lung Disease

Abstract word count: 247

Text word count: 3457

Some of the results of these studies have been previously reported in the form of a preprint (bioRxiv, 17 July 2020; <https://doi.org/10.1101/2020.07.15.20152967>).

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

This article is open access and distributed under the terms of the Creative Commons

Attribution Non-Commercial No Derivatives License 4.0

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints please contact Diane Gern (dgern@thoracic.org).

At a Glance

What is the current scientific knowledge on this subject?

The outcome of patients with ILD admitted to hospital with COVID infection and the risk factors associated with severe COVID are not known.

What does this study add to the field?

The study demonstrates that patients with ILD are at higher risk of death following COVID-19 than matched patients without ILD and the risk factors for death include male sex, an FVC less than 80% predicted and obesity.

Abstract

Rationale: The impact of COVID-19 on patients with Interstitial Lung Disease (ILD) has not been established.

Objectives: To assess outcomes in patients with ILD hospitalized for COVID-19 versus those without ILD in a contemporaneous age, sex and comorbidity matched population.

Methods: An international multicenter audit of patients with a prior diagnosis of ILD admitted to hospital with COVID-19 between 1 March and 1 May 2020 was undertaken and compared with patients, without ILD obtained from the ISARIC 4C cohort, admitted with COVID-19 over the same period. The primary outcome was survival. Secondary analysis distinguished IPF from non-IPF ILD and used lung function to determine the greatest risks of death.

Measurements and Main Results: Data from 349 patients with ILD across Europe were included, of whom 161 were admitted to hospital with laboratory or clinical evidence of COVID-19 and eligible for propensity-score matching. Overall mortality was 49% (79/161) in patients with ILD with COVID-19. After matching ILD patients with COVID-19 had higher mortality (HR 1.60, Confidence Intervals 1.17-2.18 $p=0.003$) compared with age, sex and comorbidity matched controls without ILD. Patients with a Forced Vital Capacity (FVC) of <80% had an increased risk of death versus patients with FVC $\geq 80\%$ (HR 1.72, 1.05-2.83). Furthermore, obese patients with ILD had an elevated risk of death (HR 2.27, 1.39–3.71).

Conclusions: Patients with ILD are at increased risk of death from COVID-19, particularly those with poor lung function and obesity. Stringent precautions should be taken to avoid COVID-19 in patients with ILD.

Introduction

Interstitial Lung Diseases (ILDs) represent a group of fibroinflammatory diseases affecting the alveolar interstitium of the lung. ILDs are characterized by alveolar damage and interstitial thickening and, if left untreated, lead to remorseless progression of breathlessness, cough and ultimately death from respiratory failure. The prevalence of ILDs in Europe is just under one per 1,000 people, with an annual incidence of approximately 20 per 100,000 people (1). The commonest ILD is sarcoidosis, but one of the most severe ILD is Idiopathic Pulmonary Fibrosis (IPF), a high incidence of which is found in the UK (12 per 100,000) (2, 3). IPF tends to affect older people with a mean age at diagnosis of 72 years. Men are more often affected than women. Furthermore, IPF is associated with diabetes mellitus type 2 (DMT2), hypertension (HT) and ischemic heart disease (IHD) (4, 5). People suffering from other ILDs (non-IPF ILD) tend to be younger, with a higher proportion of female sufferers, and often receive immunosuppressive therapy.

All ILDs, most notably IPF, are characterized by acute exacerbations which have a particularly high mortality rate ranging from 35-70% (6). The precise cause of acute exacerbations is unknown, but they have been associated with thoracic surgical procedures and viral infections (6). Furthermore, an acute exacerbation is associated with the development of Acute Respiratory Distress Syndrome (ARDS) which carries a high mortality and morbidity. However, there is no consensus on treatment of ARDS in this group of patients, given that mechanical ventilation is the cornerstone of supportive therapy in non-ILD patients (7).

Infection with SARS-CoV-2 may lead to COVID-19, characterized by a severe viral pneumonia and ARDS in approximately 20% of patients admitted to hospital (8). Patients most at risk of

severe COVID-19 include elderly males with comorbidities including DMT2, HT and IHD (9,10) which are shared by patients with ILD, most notably IPF (5). To understand the risk to patients with ILD hospitalized with COVID-19 and therefore the potential benefits of self-isolation during the pandemic, we undertook an international multicenter analysis of patients admitted to hospital between the 1 March and 1 May 2020 with COVID-19. We compared outcomes of patients with ILD with age, sex and comorbidity matched controls admitted with COVID-19 but without ILD, from a prospective UK cohort, the International Severe Acute Respiratory and Emerging Infection Consortium Coronavirus Clinical Characterisation Protocol (ISARIC4C CCP-UK).

Methods

Patients

Physicians admitting patients with ILD throughout Europe were contacted through research networks, e-mail contacts and social media asked to identify all patients with a pre-existing diagnosis of ILD admitted to hospital between 1st March and 1st May 2020 during the first peak of the COVID-19 pandemic. Participating centers included tertiary ILD centers from Denmark, Germany, Italy, Republic of Ireland, Spain, and the UK and secondary care hospitals from Republic of Ireland and the UK to obtain as representative a European ILD population as possible. De-identified, unlinked data from individuals were included in the audit. Each contributing site was asked to identify individuals admitted to their local hospital. As SARS-CoV-2 was an emerging virus at the start of the pandemic and PCR testing has a high false negative rate, we defined the diagnosis of COVID-19 based on a SARS-CoV-2 positive polymerase chain reaction (PCR) swab and/or clinico-radiological diagnosis. Audit data was unified with the ISARIC4C CCP-UK database, with separate categorization of

individuals who reported an existing chronic pulmonary disease. The ISARIC4C CCP-UK database is a prospective cohort study enrolling patients across the UK admitted to hospital with COVID-19. Patients admitted were identified by local investigators and followed up prospectively by clinical research staff. Detailed data on comorbidities, treatments received and outcomes were captured. The protocol is available at <https://isaric.net/ccp/>.

Data on the presence of chronic lung disease, asthma and prescription data were collected for the comparator group. Based on these variables, patients with no previous respiratory disease were selected to most accurately estimate the change in hazard for patients with ILD. Significant comorbidities of diabetes (type 1 or type 2), hypertension, chronic heart disease and malignancy, as well as immunomodulatory therapies, were recorded in both ILD audit data and the ISARIC database.

Outcomes

The primary outcome was In Hospital Mortality and other recorded outcomes were whether the patient was discharged or remained hospitalized at date of censoring (1 May 2020).

Secondary outcomes included whether patients were ventilated, or received continuous positive airway pressure, other non-invasive ventilation, or high flow oxygen and were described as 'enhanced respiratory support'. Length of stay was recorded at date of death, discharge or date of censoring. All outcomes were recorded on a standardized case report form and entered without any identifiers directly onto a secure REDcap database.

Ethics and Consent

All data were entered by the Local Clinical Care Team in anonymized fashion without linkage to any patient identifiers in line with national and local audit guidance. In the UK Health

Research Authority guidance was followed (<https://www.hra.nhs.uk/covid-19-research/guidance-using-patient-data/>), and ethical approval was not required. Similar regulations applied in Denmark, Italy, Republic of Ireland. ISARIC4C CCP-UK received ethical approval from the South Central - Oxford C Research Ethics Committee in England (Ref: 13/SC/0149), and by the Scotland A Research Ethics Committee (Ref: 20/SS/0028). Data from Spain was collected under the approval for observational studies (Ref UIC-IBU-2020-03 and PR217/20). Data from Germany were collected under approval from ethics committee of the Medical faculty of the University of Heidelberg (ref S-186/2020).

Statistical Analysis

Summary statistics are presented as frequencies and percentages for categorical data and mean (standard deviation (sd)) for normally distributed continuous data. Where continuous data were not normally distributed, the median (interquartile range [IQR]) was used.

Differences in categorical data were compared using the Chi-square test, or Fisher's exact test when expected counts were below 5 in any group. For continuous normally distributed 2-group data, we compared differences using Welch's T-test or Mann Whitney-U if data were not normally distributed. For multiple group comparisons of continuous data, we used Kruskal-Wallis tests. Data from the ILD dataset were matched in a 1:2 ratio with patients who did not have ILD from the ISARIC4C CCP-UK dataset using a nearest neighbor propensity-score matching algorithm. Patients in ISARIC4C CCP-UK with ILD were excluded to avoid double counting. We matched on confounders known to affect outcomes from COVID-19 disease including age, sex, diabetes, chronic cardiac disease, cancer, hypertension, and renal disease. Unmatched and matched populations were compared using standardized mean differences, plots and summary statistics. For survival analyses,

time was taken as admission to death (in-hospital survival) using length of stay where date was not available. Discharge from hospital was considered an absorbing state (once discharged, patients were considered no longer at risk of death). Discharged patients were not censored and included in the risk set until the end of follow-up, thus discharge did not compete with death. We generated subclasses based on the propensity-score distance and included these as terms within Cox proportional hazards models, where estimates are presented as hazards ratios, alongside the corresponding 95% confidence interval (11). Data were analyzed using R version 3.6.3 with tidyverse, matchit and finalfit packages.

Results

Baseline Demographics

Between March 1st and May 1st 2020, 349 patients with ILD were admitted to 37 hospitals throughout the UK and Europe (see supplementary Table 1). A total of 185 ILD patients had a diagnosis of COVID-19 and 161 were suitable for propensity-score matching (Figure 1). The majority of these 161 patients (114) had a positive SARS-CoV-2 PCR test, and only 47 were diagnosed clinically. Of these, 110 (68%) were male and the mean age was 73.2 (± 11.5) years. The most common ILD was IPF, with 68 (42%) patients admitted to hospital (Table 1). During the same time period, 164 patients with ILD were admitted with an alternative non-COVID diagnosis, of whom 69 (42.1%) had IPF. Overall the In Hospital Mortality (IHM) for patients with ILD and COVID-19 was 49% (79/161) compared with 17% (28/164) for patients with ILD admitted for other reasons.

Effect of ILD on outcome from COVID-19

After propensity-score matching, 161 patients with ILD were compared with 322 patients admitted to hospital between the 1st March and 1st May 2020 but without ILD, or other chronic lung disease (Table 1). There was significantly higher mortality in patients with ILD compared with non-ILD patients (49% (79/161) vs 35% (114/322) $p=0.013$) and was associated with an increased risk of death in a matched adjusted analysis (HR 1.60 CI 1.17-2.18 $p=0.003$). There was significantly higher mortality in patients with ILD compared with non-ILD patients (figure 2), which was greatest in men and increased with age, which persisted for men after adjusting for age and comorbidity (adjusted HR 1.98, 95% CI 1.14 to 3.43, $p = 0.015$). The risk of mortality was greatest in patients with IPF (HR 1.74, 95%CI 1.16 to 2.60 $p=0.007$), but a higher mortality was also seen in non-IPF ILD (HR 1.50, 95%CI 1.02 to 2.21 $p=0.040$; Figure 3a) when compared with matched patients without ILD. Of patients with non-IPF ILD, those with chronic hypersensitivity pneumonitis and rheumatoid ILD had the highest mortality (50% (7/14) and 40% (4/10) respectively), whilst those with sarcoidosis and connective tissue disease (excluding rheumatoid) related ILD had the lowest observed mortality (33% (3/9) and 23% (3/13) respectively). Overall, median length of stay in those who were still alive was not substantially different between patients without ILD (9 days [IQR 11]), compared with non-IPF ILD (10 days [IQR 8]) and IPF (10 days [IQR 8]) ($p = 0.725$) (Table 2).

Predictors of outcome from COVID-19

Obesity has been previously described to increase the risk of death from COVID-19. After obesity was included in the propensity score matching (129/161 ILD patients with data available, matched to 260 non-ILD patients), being obese and having ILD was significantly

associated with an increased hazard of death from COVID-19 (adjusted HR 2.27, 95%CI 1.39 to 3.71, $p = 0.001$; figure 3b), which was greater than the effect of obesity in non-ILD patients.

To determine whether patients with more severe ILD had a greater risk of mortality with COVID-19, the last available lung function results prior to hospital admission were analyzed. For all ILD patients, the mean Forced Vital Capacity (FVC) in patients surviving COVID-19 was 82.2% predicted compared with 76.8% predicted in patients who died ($p=0.121$). Similarly, the mean Diffusion coefficient of Carbon Monoxide (DLco) was 56.4% predicted in survivors compared with 49.6% in patients dying with COVID ($p=0.072$; Table 3). When the FVC was dichotomized using the 80% predicted threshold between mild and moderate ILD, in line with UK prescribing policy for anti-fibrotic medication, the risk of mortality was significantly higher in patients with moderate or severe ILD (HR 1.72, 95% CI 1.05-2.83), compared with mild disease (Figure 3c).

Ventilatory support for ILD patients with COVID-19

Most patients with ILD (84%; 135/161) did not receive enhanced respiratory support which was similar to matched patients without ILD (79%; 254/322; Table 2). Significantly more patients who survived did not receive enhanced respiratory support (93%, 76/82) compared with those who died (75%; 59/79 $p=0.015$). Of the 26 patients receiving enhanced respiratory support 77% (20) died, including 83% (5/6) of matched patients with ILD receiving ventilation (Table 4).

Effect of anti-fibrotic and immunosuppressive therapy on outcome from COVID-19.

In patients with ILDs 106 were taking no immunosuppressants or anti-fibrotic of whom 50% died (53/106; Table 5). Almost a third of patients with IPF (20/68) were receiving anti-fibrotic therapy at the time of admission. Seven patients were receiving pirfenidone and 13 were receiving nintedanib. Of those receiving anti-fibrotic therapy, 50% (10/20) died.

Where immunosuppressants were reported, corticosteroids were most frequently prescribed (45/55) followed by mycophenolate (17/55); overall 47% (26/55) of patients taking anti-fibrotics or immunosuppressants died. Significantly more patients with ILD received oral corticosteroids in hospital than patients without ILD (27.8% versus 9.9%; $p < 0.001$) but there was no difference in outcome between those receiving corticosteroids (48.9% mortality (22/55)) and those who did not (48.7% mortality (57/117)).

Discussion

Determining the risk of poor outcome in patients pre-existing conditions who acquire SARS-CoV-2 infection is crucial to determine what mitigation measures are required in the community. Our study shows that patients with existing interstitial lung disease were at very high risk of death when hospitalized with COVID-19, especially if they have reduced prior lung function or obesity. Most died without being offered mechanical ventilation; in those who were ventilated, mortality was very high.

Our observations were in keeping with other studies which have identified increasing age, comorbidities (Diabetes Mellitus, Ischemic Heart Disease, other non-ILD Chronic Pulmonary Diseases) and male sex as predictors of poor outcome in COVID-19 (9,12). Unfortunately, the risk for patients with ILD has not yet been quantified because patients with uncommon

diseases often do not have their specific diagnostic information recorded in large observational studies or are often not accurately reported in administrative healthcare datasets. Despite the unknown risk of COVID-19 for patients with ILD, many patients chose to self-isolate and, therefore, there appeared to be apparent 'protection' from COVID-19 observed to many ILD physicians around the world. To accurately understand the risk of COVID-19 and inform decision- and risk-matrices going forward, the European ILD community undertook an audit of hospitalized patients with ILD between the 1st March and 1st May 2020 to coincide with the first peak of COVID-19 within Europe. These data represent the largest assessment of the impact of SARS-CoV-2 infection on patients with ILD to date. These data demonstrate that patients with ILD are at increased risk of death following hospitalization for COVID-19 particularly elderly males, with poor lung function and obesity. It is notable that the risk of In Hospital Mortality from COVID-19 for patients with ILD is particularly associated with male sex and obesity. These risk factors are associated both with development of IPF, and mortality from COVID-19 in the general population, which may suggest synergy between shared mechanisms of pathogenesis (13).

The role of viral infection promoting acute exacerbations of ILD has been investigated for a number of years without a definitive answer, which probably reflects the range of viruses studied, the number of patients needed to explore such a hypothesis, and more broadly the challenges studying acute exacerbations of ILD (14,15,16,17). These data confirm that patients with ILD are at increased risk of mortality from COVID-19 compared with a matched population without ILD and the risk is greatest for IPF consistent with a respiratory virus inducing acute exacerbations of ILD.

Factors associated with poor prognosis in acute exacerbations of ILD include pulmonary fibrosis and poor lung function prior to admission and fibrotic ILDs (18,19,20,21). The data presented here, support these prior studies demonstrating that patients with a recorded FVC <80% predicted prior to admission had an increased mortality compared with those with an FVC >80%. Similarly, patients with fibrotic ILDs such as Chronic Hypersensitivity Pneumonitis had mortality rates comparable with IPF and higher than those with Sarcoid or Connective Tissue Disease associated ILD. Interestingly, obese patients with ILD had a substantially increased risk of mortality. This may reflect use of steroids in severe disease, although we do not favor this hypothesis as there was no apparent increased risk of death associated with corticosteroid use. Obesity may be due to limited activity in ILD patients, a condition that leads to progressive reduction in exercise tolerance as it becomes more severe (22). Alternatively, and perhaps most intriguingly, it may lend support to the hypothesis that severe ILD is part of the 'metabolic syndrome' (23).

This analysis also assessed respiratory support offered to patients hospitalized with ILD. In line with current practice and guidelines most patients did not receive any ventilatory support (7, 24). Most patients who survived did not require enhanced respiratory support such as High Flow Oxygen, Continuous Positive Airway Pressure or ventilation, and of those receiving enhanced respiratory support the majority died. These data continue to support the use of supportive care in preference to either non-invasive or invasive mechanical ventilation except in clearly defined cases such as predominantly inflammatory ILD or bridging to transplantation.

This analysis has a number of strengths. It is the largest, international, multicenter study to assess the outcome of patients with Interstitial Lung Disease hospitalized with the

respiratory infection SARS-Cov-2. Merging of the ILD Audit dataset with the ISARIC4C CCP-UK dataset enabled accurate, contemporary propensity-score matching for a number of potential confounding factors to assess the risk from COVID-19 disease. This enabled an assessment of the risk to patients with ILD infected with SARS-CoV-2, facilitating evidence-based mitigation strategies, such as self-isolation for this vulnerable group of patients.

This study also has some potential weaknesses. Due to the retrospective nature of the data collection recall bias might have led to over-selection of severe cases of COVID-19 in patients with ILD, however, this is mitigated by the large number of centers participating in the audit. Similarly, because only hospitalized patients could be included, it is possible that a large number of patients with ILD and COVID-19 were omitted and, therefore, the risk of COVID-19 could be over-stated. However, given the demographic associated with ILD we think this is unlikely. Also, the comparator group only included patients from the UK and some younger patients which could have led to residual confounding by geographical determinants of disease severity and treatment, however as 86% of ILD patients were recruited from UK we think this is unlikely to be a major source of confounding. Although patients with ILD were less likely to receive invasive mechanical ventilation, this is more likely due to their severe respiratory disease, however there was insufficient detail in the audit data collection to match for COVID-19 severity based on admission severity scores or provide more granularity relating to the nature of respiratory support received. However, we did not observe any patterns across the groups which were likely to have an effect. Similarly, the propensity score matching will have helped to address any imbalances which are observed within the matching variables.

The effect of obesity was assessed in the matched population suggesting an increased risk in patients without ILD, however in contrast with prior reports (9,25) no effect of obesity was observed in the control population. This reflects the limitations associated with recording obesity using inpatient data where obesity is not objectively measured as well as the relatively small numbers of patients used in the matching and the large amount of missing data relating to weight. Therefore, the data relating to obesity must be interpreted accordingly, but we believe as a modifiable risk factor it is important to highlight the risk of obesity in patients with ILD who might develop COVID-19. Finally, it was not possible to evaluate specific treatment effects, such as the use of anti-fibrotics, immunosuppressants or anti-viral therapies. The audit was undertaken in the early part of the pandemic when Hydroxychloroquine (HCQ) and remdesivir were only available in the context of clinical trials. The UK Medicine Health Regulatory Agency (MHRA) did not approve remdesivir for use in the UK until 26 May 2020 and HCQ has been shown to have no effect on outcome in any circumstance of COVID-19 infection (26,27), therefore it is highly unlikely that the results are confounded by anti-viral therapy. Only a proportion of patients received anti-fibrotics during their admission. Furthermore, due to the unknown effect of anti-fibrotics, and concerns regarding immunosuppression on the clinical course of COVID-19 there is likely to be considerable confounding due to indication. There are both potential benefits (28,29) and harms associated with background therapy for ILD (30). With specific reference to corticosteroids our analysis did not show any effect on mortality in patients with ILD. Although the RECOVERY study demonstrated an overall beneficial effect of Dexamethasone in patients with COVID-19, there was considerable heterogeneity in the response (27), and it is not clear to what extent steroid choice, steroid dosing, steroid duration, or pre-COVID-19 steroid therapy impact on outcome. However, it is reassuring from a safety perspective that

there was no obvious signal suggesting harms associated with background therapy for ILD in patients with COVID-19, although, further study to evaluate the consequence of anti-fibrotic and immunomodulatory therapy in ILD are needed.

In summary, these data demonstrate that patients with ILD, particularly those with fibrotic ILD are at higher risk of mortality from COVID-19 than patients without ILD. Furthermore, the risk is heightened in elderly males, those with obesity or poor lung function and we would recommend dietary advice in overweight patients. We also propose that patients with ILD, particularly severe fibrotic ILD, continue to be regarded as high risk of mortality from COVID-19 and follow national self-isolation guidelines for vulnerable individuals and be prioritized for SARS-CoV-2 vaccination at such time as it becomes available. Finally, we believe these data demonstrate the importance of international collaboration to collect data to understand the consequences of emerging threats to patients with ILD.

References

- 1) Boris Duchemann, Isabella Annesi-Maesano, Camille Jacobe de Naurois, Shreosi Sanyal, Pierre-Yves Brillet, Michel Brauner, Marianne Kambouchner, Sophie Huynh, Jean Marc Naccache, Raphael Borie, Jacques Piquet, Arsène Mekinian, Jérôme Virally, Yurdagul Uzunhan, Jacques Cadranel, Bruno Crestani, Olivier Fain, Francois Lhote, Robin Dhote, Nathalie Saidenberg-Kermanac'h, Paul-André Rosental, Dominique Valeyre, Hilario Nunes. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. *European Respiratory Journal* 2017 50: 1602419; DOI: 10.1183/13993003.02419-2016
- 2) The citation is from IPF Statistics: Respiratory Health of the Nation project 2016. Accessed from <https://www.blf.org.uk/support-for-you/idiopathic-pulmonary-fibrosis-ipf/statistics> on 01/10/2020
- 3) Amy L. Olson, Alex H. Gifford, Naohiko Inase, Evans R. Fernández Pérez, Takafumi Suda. The epidemiology of idiopathic pulmonary fibrosis and interstitial lung diseases at risk of a progressive-fibrosing phenotype. *European Respiratory Review* 2018 27: 180077; DOI: 10.1183/16000617.0077-2018.
- 4) Kreuter M, Ehlers-Tenenbaum S, Palmowski K, Bruhwylter J, Oltmanns U, Muley T, Heussel CP, Warth A, Kolb M, Herth FJF. Impact of Comorbidities on Mortality in Patients with Idiopathic Pulmonary Fibrosis. In: Wu M, editor. *PLoS One* 2016;11:e0151425.
- 5) Hyldgaard C, Hilberg O, Bendstrup E. How does comorbidity influence survival in idiopathic pulmonary fibrosis? *Respir Med* 2014;108:647–53.

- 6) Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, Lee JS, Maher TM, Wells AU, Antoniou KM, Behr J, Brown KK, Cottin V, Flaherty KR, Fukuoka J, Hansell DM, Johkoh T, Kaminski N, Kim DS, Kolb M, Lynch DA, Myers JL, Raghu G, Richeldi L, Taniguchi H, Martinez FJ. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. *Am J Respir Crit Care Med*. 2016 Aug 1;194(3):265-75. doi: 10.1164/rccm.201604-0801CI.
- 7) Kreuter M, Polke M, Walsh SLF, Krisam J, Collard HR, Chaudhuri N, Avdeev S, Behr J, Calligaro G, Corte T, Flaherty K, Funke-Chambour M, Kolb M, Kondoh Y, Maher TM, Molina Molina M, Morais A, Moor CC, Morisset J, Pereira C, Quadrelli S, Selman M, Tzouvelekis A, Valenzuela C, Vancheri C, Vicens-Zygmunt V, Wälscher J, Wuyts W, Wijsenbeek M, Cottin V, Bendstrup E. Acute exacerbation of idiopathic pulmonary fibrosis: international survey and call for harmonisation. *Eur Respir J*. 2020 Apr 3;55(4):1901760. doi: 10.1183/13993003.01760-2019.
- 8) Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, Alvarado-Arnez LE, Bonilla-Aldana DK, Franco-Paredes C, Henao-Martinez AF, Paniz-Mondolfi A, Lagos-Grisales GJ, Ramírez-Vallejo E, Suárez JA, Zambrano LI, Villamil-Gómez WE, Balbin-Ramon GJ, Rabaan AA, Harapan H, Dhama K, Nishiura H, Kataoka H, Ahmad T, Sah R; Latin American Network of Coronavirus Disease 2019-COVID-19 Research (LANCOVID-19). Electronic address: <https://www.lancovid.org>. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med Infect Dis*. 2020 Mar-Apr;34:101623. doi:10.1016/j.tmaid.2020.101623.

- 9) Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read JM, Dondelinger F, Carson G, Merson L, Lee J, Plotkin D, Sigfrid L, Halpin S, Jackson C, Gamble C, Horby PW, Nguyen-Van-Tam JS, Ho A, Russell CD, Dunning J, Openshaw PJ, Baillie JK, Semple MG; ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ*. 2020 May 22;369:m1985. doi: 10.1136/bmj.m1985.
- 10) Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020 Mar 28;395(10229):1054-1062. doi: 10.1016/S0140-6736(20)30566-3.
- 11) Ho DE, Imai K, King G, Stuart EA. Matching as Nonparametric Preprocessing for Reducing Model Dependence in Parametric Causal Inference *Political Analysis* (2007) 15:199–236 doi:10.1093/pan/mpi013
- 12) Banerjee A, Pasea L, Harris S, Gonzalez-Izquierdo A, Torralbo A, Shallcross L, Noursadeghi M, Pillay D, Sebire N, Holmes C, Pagel C, Wong WK, Langenberg C, Williams B, Denaxas S, Hemingway H. Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study. *Lancet*. 2020 May 30;395(10238):1715-1725. doi: 10.1016/S0140-6736(20)30854-0. Epub 2020 May 12.

- 13) Jenkins G. Demystifying Pulmonary Fibrosis. *Am J Physiol Lung Cell Mol Physiol*. 2020 Aug 5. doi: 10.1152/ajplung.00365.2020.
- 14) Ushiki A, Yamazaki Y, Hama M, Yasuo M, Hanaoka M, Kubo K. Viral infections in patients with an acute exacerbation of idiopathic interstitial pneumonia. *Respir Investig*. 2014 Jan;52(1):65-70. doi: 10.1016/j.resinv.2013.07.005. Epub 2013 Aug 12.
- 15) Saraya T, Kimura H, Kurai D, Tamura M, Ogawa Y, Mikura S, Sada M, Oda M, Watanabe T, Ohkuma K, Inoue M, Honda K, Watanabe M, Yokoyama T, Fujiwara M, Ishii H, Takizawa H. Clinical significance of respiratory virus detection in patients with acute exacerbation of interstitial lung diseases. *Respir Med*. 2018 Mar;136:88-92. doi: 10.1016/j.rmed.2018.02.003. Epub 2018 Feb 8.
- 16) Weng D, Chen XQ, Qiu H, Zhang Y, Li QH, Zhao MM, Wu Q, Chen T, Hu Y, Wang LS, Wei YR, Du YK, Chen SS, Zhou Y, Zhang F, Shen L, Su YL, Kolb M, Li HP. The Role of Infection in Acute Exacerbation of Idiopathic Pulmonary Fibrosis. *Mediators Inflamm*. 2019 Jan 3;2019:5160694. doi: 10.1155/2019/5160694. eCollection 2019.
- 17) Sheng G, Chen P, Wei Y, Yue H, Chu J, Zhao J, Wang Y, Zhang W, Zhang HL. Viral Infection Increases the Risk of Idiopathic Pulmonary Fibrosis: A Meta-Analysis. *Chest*. 2020 May;157(5):1175-1187. doi: 10.1016/j.chest.2019.10.032. Epub 2019 Nov 12.
- 18) Qiu M, Chen Y, Ye Q. Risk factors for acute exacerbation of idiopathic pulmonary fibrosis: A systematic review and meta-analysis. *Clin Respir J*. 2018 Mar;12(3):1084-1092. doi: 10.1111/crj.12631. Epub 2017 Apr 12.

- 19) Enomoto N, Naoi H, Aono Y, Katsumata M, Horiike Y, Yasui H, Karayama M, Hozumi H, Suzuki Y, Furuhashi K, Fujisawa T, Inui N, Nakamura Y, Suda T. Acute exacerbation of unclassifiable idiopathic interstitial pneumonia: comparison with idiopathic pulmonary fibrosis. *Ther Adv Respir Dis*. 2020 Jan-Dec;14:1753466620935774. doi: 10.1177/1753466620935774.
- 20) Taya T, Chiba H, Yamada G, Takahashi M, Ikeda K, Mori Y, Otsuka M, Takahashi H. Risk factors for acute exacerbation of idiopathic interstitial pneumonia in patients undergoing lung cancer treatment. *Jpn J Clin Oncol*. 2019 Dec 27;49(12):1126-1133. doi: 10.1093/jjco/hyz115.
- 21) Enomoto N, Oyama Y, Enomoto Y, Mikamo M, Karayama M, Hozumi H, Suzuki Y, Kono M, Furuhashi K, Fujisawa T, Inui N, Nakamura Y, Suda T. Prognostic evaluation of serum ferritin in acute exacerbation of idiopathic pulmonary fibrosis. *Clin Respir J*. 2018 Aug;12(8):2378-2389. doi: 10.1111/crj.12918.
- 22) Bahmer T, Kirsten AM, Waschki B, Rabe KF, Magnussen H, Kirsten D, Marco Gramm M, Hummler S, Brunnemer E, Kreuter M, Watz H. Prognosis and longitudinal changes of physical activity in idiopathic pulmonary fibrosis. *BMC Pulm Med*. 2017; 17: 104. doi: 10.1186/s12890-017-0444-0
- 23) Papaioannou O, Karampitsakos T, Barbayianni I, Chrysikos S, Xylourgidis N, Tzilas V, Bouros D, Aidinis V, Tzouvelekis A. Metabolic Disorders in Chronic Lung Diseases. *Front Med (Lausanne)*. 2018 Jan 18;4:246. doi: 10.3389/fmed.2017.00246. eCollection 2017.

- 24) Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE Jr, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schönemann HJ; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011 Mar 15;183(6):788-824. doi: 10.1164/rccm.2009-040GL.
- 25) Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, Aaron JG, Claassen J, Rabbani LE, Hastie J, Hochman BR, Salazar-Schicchi J, Yip NH, Brodie D, O'Donnell MR. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020 Jun 6;395(10239):1763-1770. doi: 10.1016/S0140-6736(20)31189-2. Epub 2020 May 19.
- 26) Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, Skipper CP, Nascene AA, Nicol MR, Abassi M, Engen NW, Cheng MP, LaBar D, Lother SA, MacKenzie LJ, Drobot G, Marten N, Zarychanski R, Kelly LE, Schwartz IS, McDonald EG, Rajasingham R, Lee TC, Hullsiek KH. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. *N Engl J Med*. 2020 Aug 6;383(6):517-525. doi: 10.1056/NEJMoa2016638. Epub 2020 Jun 3.
- 27) Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, Damiani LP, Marcadenti A, Kawano-Dourado L, Lisboa T, Junqueira DLM, de Barros E Silva PGM, Tramujas L, Abreu-Silva EO, Laranjeira LN, Soares AT, Echenique LS, Pereira AJ, Freitas FGR, Gebara OCE, Dantas VCS, Furtado RHM, Milan EP, Golin NA, Cardoso FF,

Maia IS, Hoffmann Filho CR, Kormann APM, Amazonas RB, Bocchi de Oliveira MF, Serpa-Neto A, Falavigna M, Lopes RD, Machado FR, Berwanger O; Coalition Covid-19 Brazil I Investigators. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *N Engl J Med*. 2020 Jul 23;NEJMoa2019014. doi: 10.1056/NEJMoa2019014. Online ahead of print.

28) George PM, Wells AU, Jenkins RG. Pulmonary Fibrosis and COVID-19: The Potential Role for Antifibrotic Therapy *Lancet Respir Med* 2020 May 15;S2213-2600(20)30225-3. doi: 10.1016/S2213-2600(20)30225-3. Online ahead of print.

29) Peter Horby, Wei Shen Lim, Jonathan Emberson, Marion Mafham, Jennifer Bell, Louise Linsell, Natalie Staplin, Christopher Brightling, Andrew Ustianowski, Einas Elmahi, Benjamin Prudon, Christopher Green, Timothy Felton, David Chadwick, Kanchan Rege, Christopher Fegan, Lucy C Chappell, Saul N Faust, Thomas Jaki, Katie Jeffery, Alan Montgomery, V Kathryn Rowan, Edmund Juszczak, J Kenneth Baillie, Richard Haynes, Martin J Landray, RECOVERY Collaborative Group. Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report *MedRxiv* doi: [10.1101/2020.06.22.20137273](https://doi.org/10.1101/2020.06.22.20137273).

30) Clausen ES, Zaffiri L. Infection prophylaxis and management of viral infection. *Ann Transl Med*. 2020 Mar;8(6):415. doi: 10.21037/atm.2019.11.85.

Funding

RGJ is supported by an NIHR Research Professor Award (RP-2017-08-ST2-014). LPH is supported by the NIHR Oxford Biomedical Research Centre. This work is supported by grants from: the National Institute for Health Research [award CO-CIN-01], the Medical Research Council [grant MC_PC_19059] and by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Emerging and Zoonotic Infections at University of Liverpool in partnership with Public Health England (PHE), in collaboration with Liverpool School of Tropical Medicine and the University of Oxford [NIHR award 200907], Wellcome Trust and Department for International Development [215091/Z/18/Z], and the Bill and Melinda Gates Foundation [OPP1209135], and Liverpool Experimental Cancer Medicine Centre for providing infrastructure support for this research (Grant Reference: C18616/A25153). The views expressed are those of the authors and not necessarily those of the DHSC, DID, NIHR, MRC, Wellcome Trust or PHE.

ISARIC 4C Investigators

Consortium Lead Investigator: J Kenneth Baillie, Chief Investigator: Malcolm G Semple, Co-Lead Investigator: Peter JM Openshaw. ISARIC Clinical Coordinator: Gail Carson.

Co-Investigators: Beatrice Alex, Benjamin Bach, Wendy S Barclay, Debby Bogaert, Meera Chand, Graham S Cooke, Annemarie B Docherty, Jake Dunning, Ana da Silva Filipe, Tom Fletcher, Christopher A Green, Ewen M Harrison, Julian A Hiscox, Antonia Ying Wai Ho, Peter W Horby, Samreen Ijaz, Saye Khoo, Paul Klenerman, Andrew Law, Wei Shen Lim, Alexander J Mentzer, Laura Merson, Alison M Meynert, Mahdad Noursadeghi, Shona C Moore, Massimo Palmarini, William A Paxton, Georgios Pollakis, Nicholas Price, Andrew

Rambaut, David L Robertson, Clark D Russell, Vanessa Sancho-Shimizu, Janet T Scott, Thushan de Silva, Louise Sigfrid, Tom Solomon, Shiranee Sriskandan, David Stuart, Charlotte Summers, Richard S Tedder, Emma C Thomson, AA Roger Thompson, Ryan S Thwaites, Lance CW Turtle, Maria Zambon.

Project Managers: Hayley Hardwick, Chloe Donohue, Ruth Lyons, Fiona Griffiths, Wilna Oosthuyzen.

Data Analysts: Lisa Norman, Riinu Pius, Tom M Drake, Cameron J Fairfield, Stephen Knight, Kenneth A Mclean, Derek Murphy, Catherine A Shaw.

Data and Information System Manager: Jo Dalton, Michelle Girvan, Egle Saviciute, Stephanie Roberts, Janet Harrison, Laura Marsh, Marie Connor, Sophie Halpin, Clare Jackson, Carrol Gamble.

Data integration and presentation: Gary Leeming, Andrew Law, Murray Wham, Sara Clohisey, Ross Hendry, James Scott-Brown.

Material Management: William Greenhalf, Victoria Shaw, Sarah McDonald.

Patient engagement: Seán Keating

Outbreak Laboratory Staff and Volunteers: Katie A. Ahmed, Jane A Armstrong, Milton Ashworth, Innocent G Asimwe, Siddharth Bakshi, Samantha L Barlow, Laura Booth, Benjamin Brennan, Katie Bullock, Benjamin WA Catterall, Jordan J Clark, Emily A Clarke, Sarah Cole, Louise Cooper, Helen Cox, Christopher Davis, Oslem Dincarslan, Chris Dunn, Philip Dyer, Angela Elliott, Anthony Evans, Lorna Finch, Lewis WS Fisher, Terry Foster, Isabel Garcia-Dorival, William Greenhalf, Philip Gunning, Catherine Hartley, Antonia Ho,

Rebecca L Jensen, Christopher B Jones, Trevor R Jones, Shadia Khandaker, Katharine King, Robyn T. Kiy, Chrysa Koukorava, Annette Lake, Suzannah Lant, Diane Latawiec, L Lavelle-Langham, Daniella Lefteri, Lauren Lett, Lucia A Livoti, Maria Mancini, Sarah McDonald, Laurence McEvoy, John McLauchlan, Soeren Metelmann, Nahida S Miah, Joanna Middleton, Joyce Mitchell, Shona C Moore, Ellen G Murphy, Rebekah Penrice-Randal, Jack Pilgrim, Tessa Prince, Will Reynolds, P. Matthew Ridley, Debby Sales, Victoria E Shaw, Rebecca K Shears, Benjamin Small, Krishanthi S Subramaniam, Agnieska Szemiel, Aislynn Taggart, Jolanta Tanianis-Hughes, Jordan Thomas, Erwan Trochu, Libby van Tonder, Eve Wilcock, J. Eunice Zhang.

Local Principal Investigators: Kayode Adeniji, Daniel Agranoff, Ken Agwuh, Dhiraj Ail, Ana Alegria, Brian Angus, Abdul Ashish, Dougal Atkinson, Shahedal Bari, Gavin Barlow, Stella Barnass, Nicholas Barrett, Christopher Bassford, David Baxter, Michael Beadsworth, Jolanta Bernatoniene, John Berridge, Nicola Best, Pieter Bothma, David Brealey, Robin Brittain-Long, Naomi Bulteel, Tom Burden, Andrew Burtenshaw, Vikki Caruth, David Chadwick, Duncan Chambler, Nigel Chee, Jenny Child, Srikanth Chukkambotla, Tom Clark, Paul Collini, Catherine Cosgrove, Jason Cupitt, Maria-Teresa Cutino-Moguel, Paul Dark, Chris Dawson, Samir Dervisevic, Phil Donnison, Sam Douthwaite, Ingrid DuRand, Ahilanadan Dushianthan, Tristan Dyer, Cariad Evans, Chi Eziefula, Chrisopher Fegan, Adam Finn, Duncan Fullerton, Sanjeev Garg, Sanjeev Garg, Atul Garg, Effrossyni Gkrania-Klotsas, Jo Godden, Arthur Goldsmith, Clive Graham, Elaine Hardy, Stuart Hartshorn, Daniel Harvey, Peter Havalda, Daniel B Hawcutt, Maria Hobrok, Luke Hodgson, Anita Holme, Anil Hormis, Michael Jacobs, Susan Jain, Paul Jennings, Agilan Kaliappan, Vidya Kasipandian, Stephen Kegg, Michael Kelsey, Jason Kendall, Caroline Kerrison, Ian

Kerslake, Oliver Koch, Gouri Koduri, George Koshy, Shondipon Laha, Steven Laird, Susan Larkin, Tamas Leiner, Patrick Lillie, James Limb, Vanessa Linnett, Jeff Little, Michael MacMahon, Emily MacNaughton, Ravish Mankregod, Huw Masson, Elijah Matovu, Katherine McCullough, Ruth McEwen, Manjula Meda, Gary Mills, Jane Minton, Mariyam Mirfenderesky, Kavya Mohandas, Quen Mok, James Moon, Elinoor Moore, Patrick Morgan, Craig Morris, Katherine Mortimore, Samuel Moses, Mbiye Mpenge, Rohinton Mulla, Michael Murphy, Megan Nagel, Thapas Nagarajan, Mark Nelson, Igor Otahal, Mark Pais, Selva Panchatsharam, Hassan Paraiso, Brij Patel, Justin Pepperell, Mark Peters, Mandeep Phull, Stefania Pintus, Jagtur Singh Pooni, Frank Post, David Price, Rachel Prout, Nikolas Rae, Henrik Reschreiter, Tim Reynolds, Neil Richardson, Mark Roberts, Devender Roberts, Alistair Rose, Guy Rousseau, Brendan Ryan, Taranprit Saluja, Aarti Shah, Prad Shanmuga, Anil Sharma, Anna Shawcross, Jeremy Sizer, Manu Shankar-Hari, Richard Smith, Catherine Snelson, Nick Spittle, Nikki Staines, Tom Stambach, Richard Stewart, Pradeep Subudhi, Tamas Szakmany, Kate Tatham, Jo Thomas, Chris Thompson, Robert Thompson, Ascanio Tridente, Darell Tupper-Carey, Mary Twagira, Andrew Ustianowski, Nick Vallotton, Lisa Vincent-Smith, Shico Visuvanathan, Alan Vuylsteke, Sam Waddy, Rachel Wake, Andrew Walden, Ingeborg Welters, Tony Whitehouse, Paul Whittaker, Ashley Whittington, Meme Wijesinghe, Martin Williams, Lawrence Wilson, Sarah Wilson, Stephen Winchester, Martin Wiselka, Adam Wolverson, Daniel G Wooton, Andrew Workman, Bryan Yates, and Peter Young.

Acknowledgements

This work uses data provided by patients and collected by the NHS as part of their care and support #DataSavesLives. We are extremely grateful to the 2,648 frontline NHS

clinical and research staff and volunteer medical students, who collected this data in challenging circumstances; and the generosity of the participants and their families for their individual contributions in these difficult times. We also acknowledge the support of Jeremy J Farrar, Nahoko Shindo, Devika Dixit, Nipunie Rajapakse, Lyndsey Castle, Martha Buckley, Debbie Malden, Katherine Newell, Kwame O'Neill, Emmanuelle Denis, Claire Petersen, Scott Mullaney, Sue MacFarlane, Nicole Maziere, Julien Martinez, Oslem Dincarslan, and Annette Lake. We would like to thank Mustafa Al-Zubaidy, Hayoung Lee, Oliver Awad, Verity Loake, Anex Wilson, Lise-Ann Grundy, Mark Major and Amanda Bell who collected data.

Figure Legends

Figure 1 Audit Flow Diagram showing patients recruited and flow to matching.

Figure 1

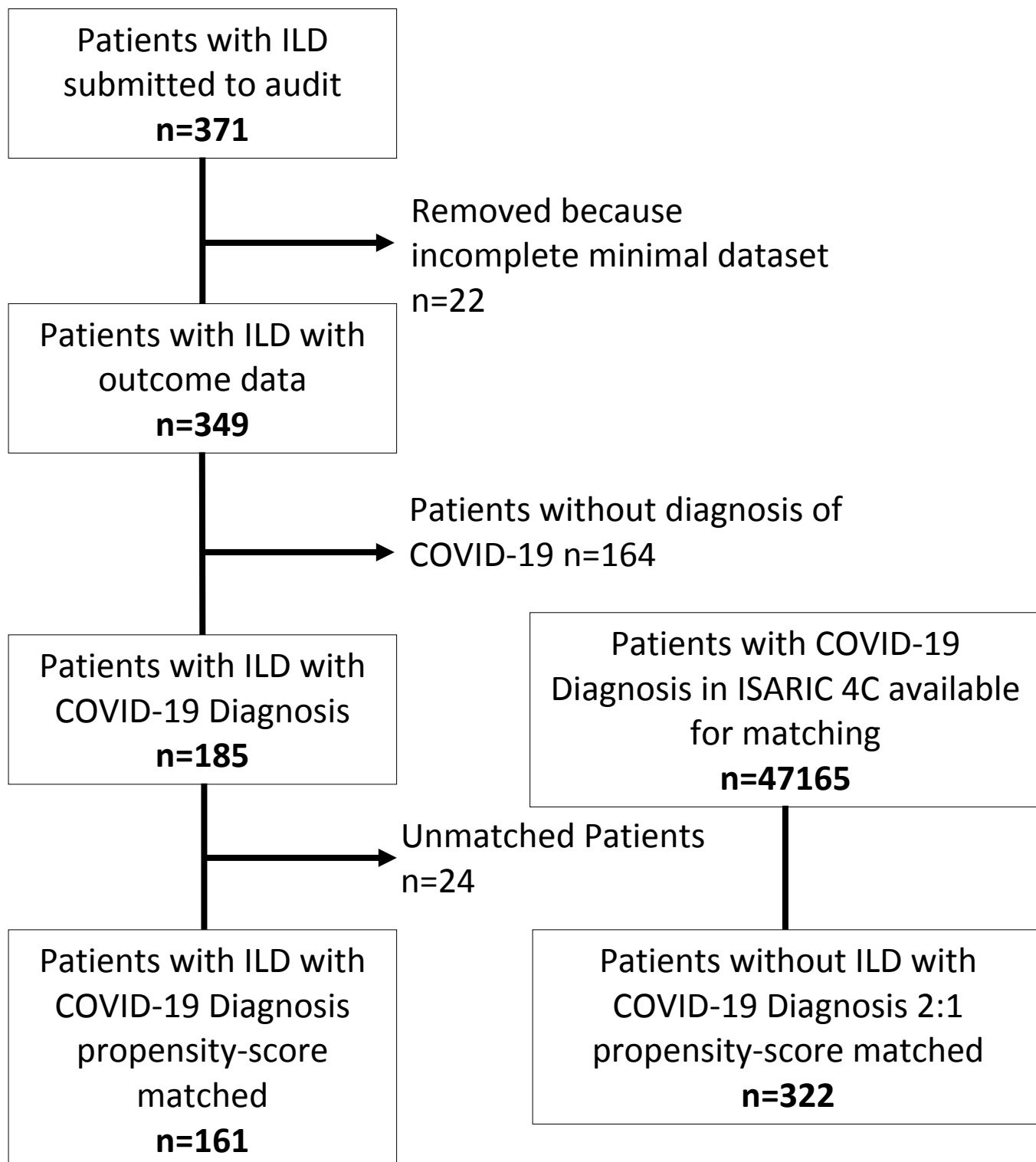


Figure 2 A) In Hospital Mortality with 95% confidence intervals for female ILD patients hospitalized with COVID-19 stratified by age compared with those without ILD. B) In Hospital Mortality with 95% confidence intervals for male ILD patients hospitalized with COVID-19 stratified by age compared with those without ILD.

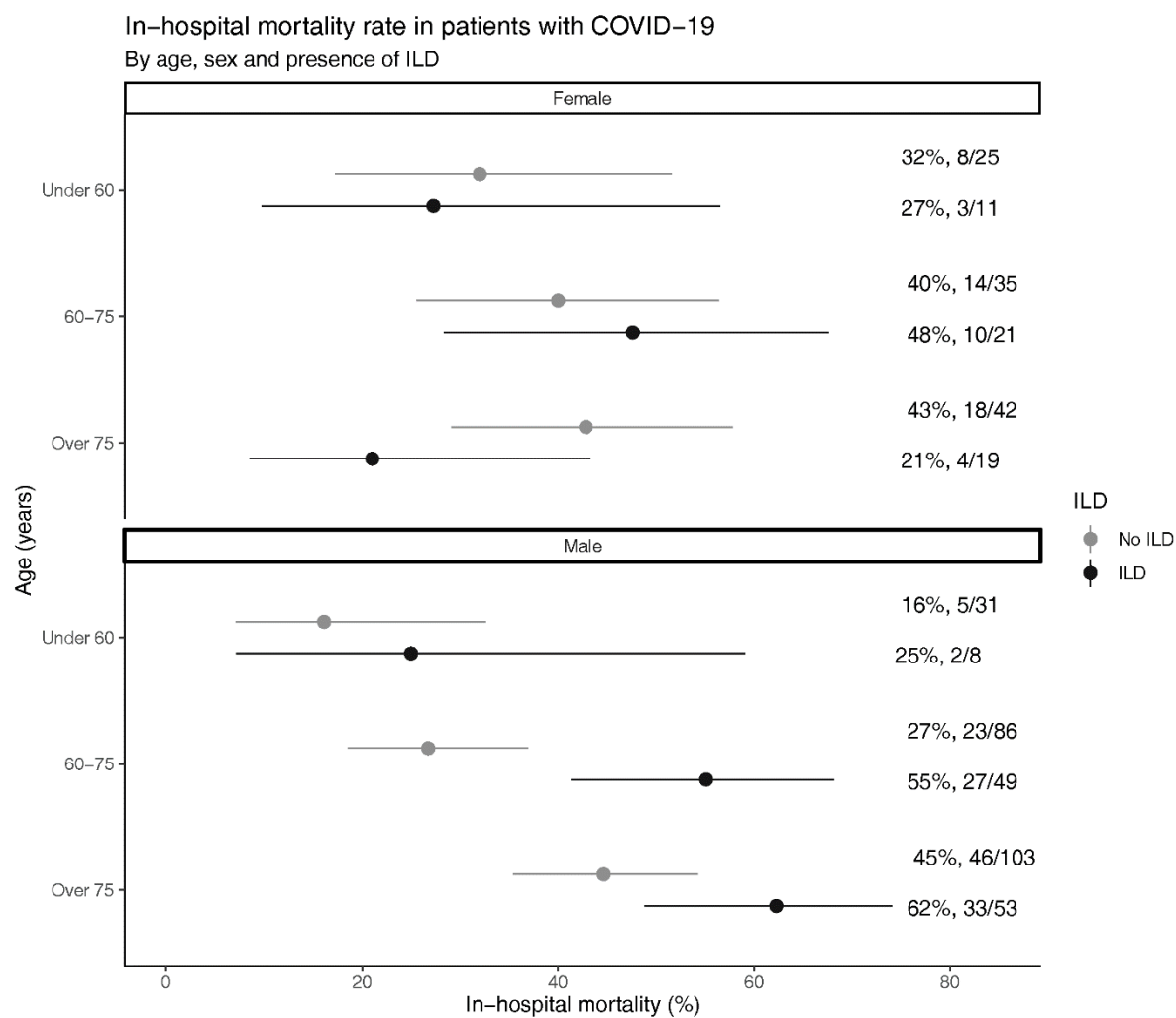


Figure 3 A) Effect of ILD on mortality following COVID-19 (Propensity Matched), B) effect of obesity and ILD (Propensity Matched) C) and effect of FVC on outcome in ILD patients only.

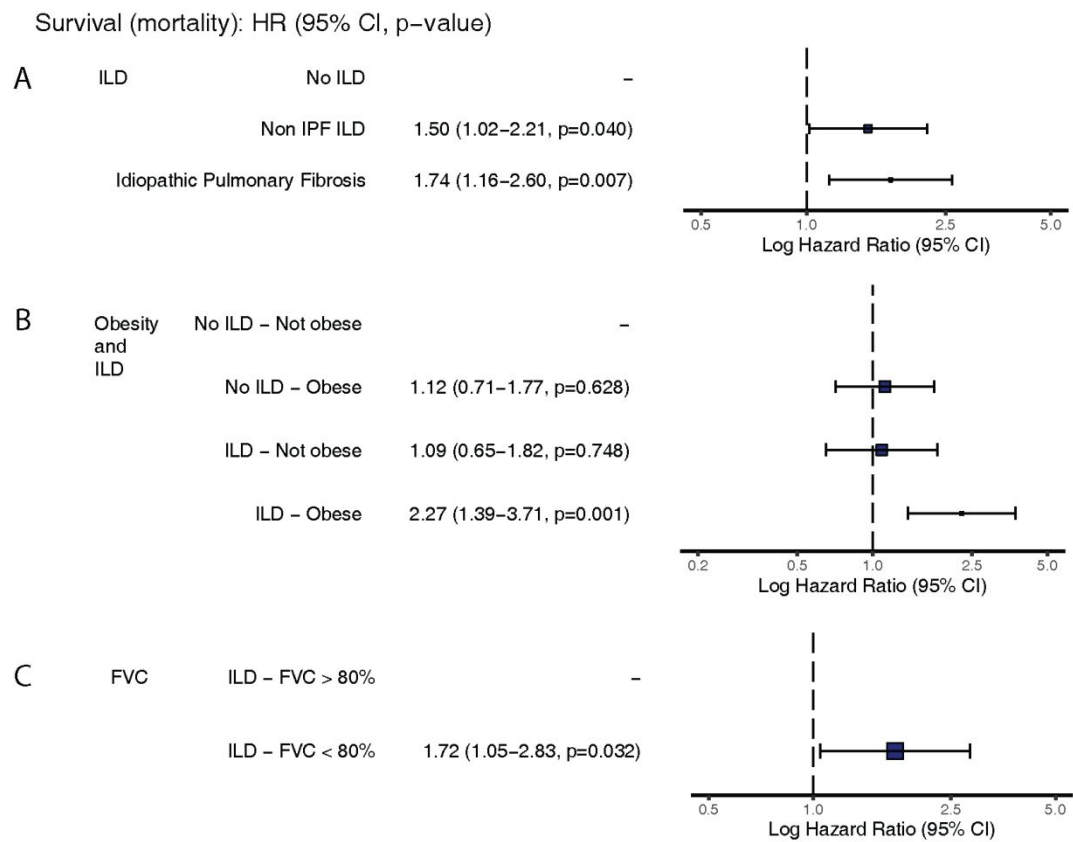


Table 1 – Patient Characteristics by ILD

	Total N	levels	No ILD	ILD	p
Total N (%)			322 (66.7)	161 (33.3)	
Age (years)	483	Mean (SD)	72.6 (13.4)	73.2 (11.5)	0.639*
Age categories	483	<50	10 (3.1)	5 (3.1)	1.000
		50-69	112 (34.8)	56 (34.8)	
		70-79	96 (29.8)	48 (29.8)	
		80+	104 (32.3)	52 (32.3)	
Sex at Birth	483	Male	220 (68.3)	110 (68.3)	1.000
ILD	483	Chronic	0 (0.0)	14 (8.7)	
		Hypersensitivity Pneumonitis			
		Connective Tissue Disease	0 (0.0)	13 (8.1)	
		related ILD			
		Idiopathic Pulmonary Fibrosis	0 (0.0)	68 (42.2)	
		Other	0 (0.0)	47 (29.2)	
		Rheumatoid related ILD	0 (0.0)	10 (6.2)	
		Sarcoidosis	0 (0.0)	9 (5.6)	
Chronic Cardiac Disease	483	Yes	92 (28.6)	46 (28.6)	1.000
Diabetes	483	Yes	98 (30.4)	49 (30.4)	1.000
Malignant neoplasm	483	Yes	56 (17.4)	28 (17.4)	1.000
Obesity	419	Yes (Missing)	23 (7.1) 32 (9.9)	45 (28.0) 32 (19.9)	<0.001
Hypertension	483	Yes	148 (46.0)	74 (46.0)	1.000
Chronic kidney disease	483	Yes	16 (5.0)	8 (5.0)	1.000
Pirfenidone	483	Yes	0 (0.0)	7 (4.3)	
Nintedanib	483	Yes	0 (0.0)	13 (8.1)	
Corticosteroids	483	Yes	28 (8.7)	45 (28.0)	<0.001

ILD- Interstitial Lung Disease. SD – Standard Deviation. All test Chi-square unless indicated by * where Welch's two sample t-test used.

Table 2: Outcomes by ILD

	Total N	levels	No ILD	ILD	p
Died	483	Died	114 (35.4)	79 (49.1)	0.013
Respiratory Support	483	Unenhanced	254 (78.9)	136 (84.5)	0.288
		Enhanced	39 (12.1)	20 (12.4)	
		Respiratory Support Ventilation	29 (9.0)	6 (3.7)	
Length of stay for those alive	290	Median (IQR)	9.0 (11.0)	10.0 (8.0)	0.725**

IQR – Interquartile range. All test Chi-square unless indicated by *Standard flow-rate Oxygen supplementation not considered ‘enhanced’ respiratory support, CPAP and High Flow O₂ considered enhanced respiratory support. **where Kruskal Wallis used.

Table 3 – Lung function in ILD group by outcome

label	Total N		Alive	Died	p
Forced Vital Capacity	147	Mean (SD)	2.7 (1.0)	2.6 (0.9)	0.372*
Forced Vital Capacity, percentage of predicted	151	Mean (SD)	82.2 (23.0)	76.8 (21.0)	0.135*
Forced Vital Capacity, at 80% of predicted	151	FVC < 80%	35 (42.7)	42 (60.9)	0.039
		FVC > 80%	47 (57.3)	27 (39.1)	
Forced Vital Capacity, percentage of predicted	151	<50%	7 (6.9)	4 (4.8)	0.070
		50 to 80%	28 (27.7)	38 (45.8)	
		80 to 100%	33 (32.7)	17 (20.5)	
		Over 100%	14 (13.9)	10 (12.0)	
Diffusing capacity for carbon monoxide	81	Mean (SD)	5.2 (3.4)	4.2 (1.9)	0.093*
Diffusing capacity for carbon monoxide, percentage of predicted	122	Mean (SD)	56.4 (19.4)	49.6 (21.6)	0.072*

All ILD patients including those unmatched. SD – Standard Deviation. All tests Welch's two sample t-test, unless indicated by * where Kruskal Wallis used.

Table 4: Use of Ventilation in patients with ILD by outcome

	Total N		Alive	Died	p
Respiratory Support	161	Unenhanced respiratory support*	76 (92.7)	59 (74.7)	0.015
		Enhanced Respiratory Support	5 (6.0)	15 (23)	0.005
		Ventilation	1 (1.2)	5 (3.8)	0.190

All test Chi-square. *Standard flow-rate Oxygen supplementation not considered 'enhanced' respiratory support, CPAP and High Flow O₂ considered enhanced respiratory support. Note a further 10 patients with ILD were ventilated but not included in the matched cohort, of those 6 survived.

Table 5: Drugs received by patients with ILD in matched cohort (n=161)

	levels	Alive	Died
Received Immuno- suppressants/ Anti-fibrotics	Yes	29 (34.9)	26 (32.9)
Methotrexate/ Azathioprine	Yes	3 (3.6)	2 (1.3)
Nintedanib	Yes	9 (10.8)	4 (5.1)
Pirfenidone*	Yes	1 (1.2)	6 (7.6)
Mycophenolate	Yes	10 (12.0)	7 (8.9)
Corticosteroid	Yes	23 (27.7)	22 (27.8)

*2 further patients received pirfenidone and survived but were not included in matched cohort.

Outcome of Hospitalization for COVID-19 in Patients with Interstitial Lung Disease: An International Multicenter Study

Supplementary Table 1

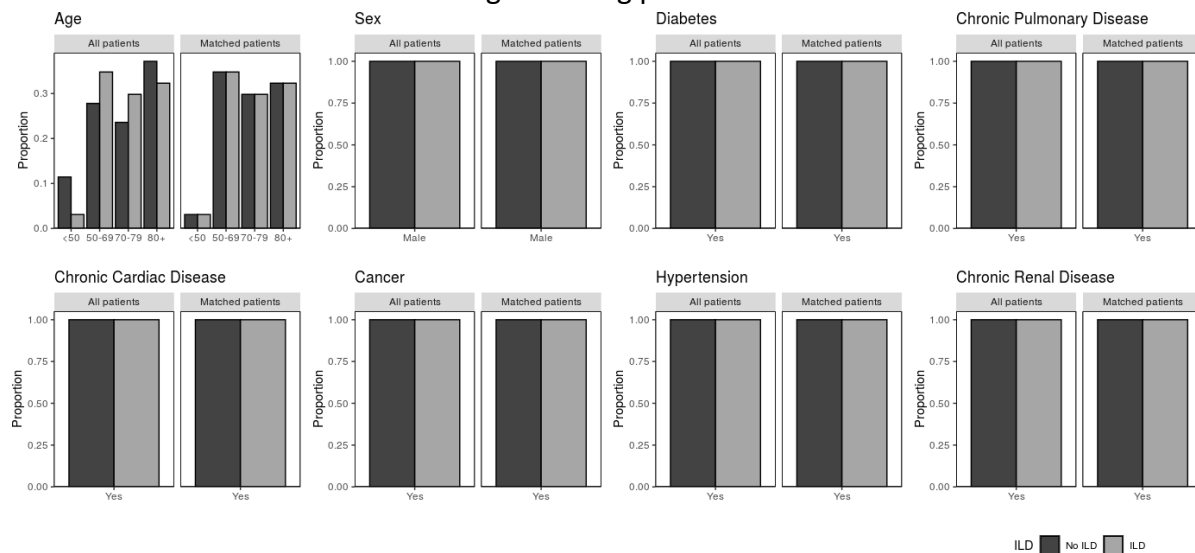
COUNTRY	NUMBER	PERCENTAGE
UK	299	86
REPUBLIC OF IRELAND	11	3
SPAIN	27	7.5
GERMAN	5	1.5
ITALY	5	1.5
DENMARK	<3	<1

Supplementary Table 2

label	'Other' ILD diagnoses	n
Other ILD Details	Age-related ILD/presbyotic lung	<3
	ANCA vasculitis	<3
	asbestosis	5
	Autoimmune Pneumonitis	5
	Chronic eosinophilic pneumonia	<3
	Combined Emphysema and Pulmonary Fibrosis	7
	Desquamative Intestinal Pneumonia	<3
	Non-Specific Interstitial Pneumonia	10
	Organising Pneumonia	<3
	PPFE	<3
	smoking related ILD	<3
	Unclassifiable ILD	11

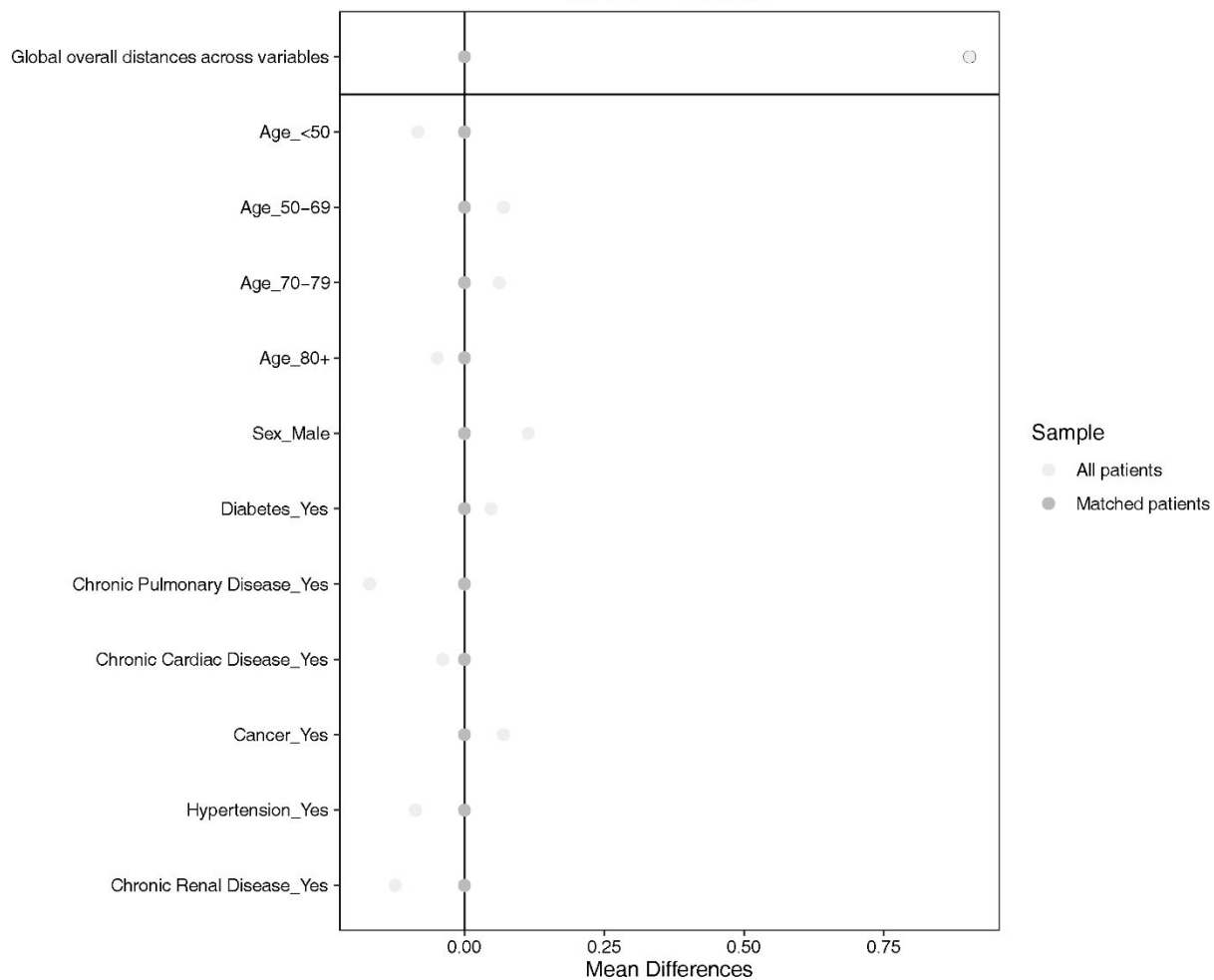
Supplemental Figure
Figure S1 Balance Plots

Distribution of differences across ILD groups by matching variable. Propensity score matching normalised standardized mean differences across the treatment groups, with observed differences before matching not being present after.



ILD No ILD ILD

Covariate Balance



Sample
 All patients
 Matched patients

Figure S2 Impact of sex, and co-morbidity on outcomes of COVID-19 in ILD]

Survival (mortality): HR (95% CI, p-value)

Age (per year increase)	-	1.01 (0.99-1.02, p=0.565)
Sex at Birth	Female	-
	Male	1.98 (1.14-3.43, p=0.015)
Chronic Cardiac Disease	No	-
	Yes	0.98 (0.60-1.60, p=0.942)
Diabetes	No	-
	Yes	1.24 (0.77-2.00, p=0.377)
Hypertension	No	-
	Yes	0.95 (0.60-1.50, p=0.817)

