Outcome of hospitalization for COVID-19 in patients with Interstitial Lung Disease: An international multicenter study.

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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 co-morbidity matched controls without ILD. Patients with a Forced Vital Capacity (FVC) of <80% had an increased risk of death versus patients with FVC ≥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 Kruskall-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.

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Figure Legends

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

Figure 1

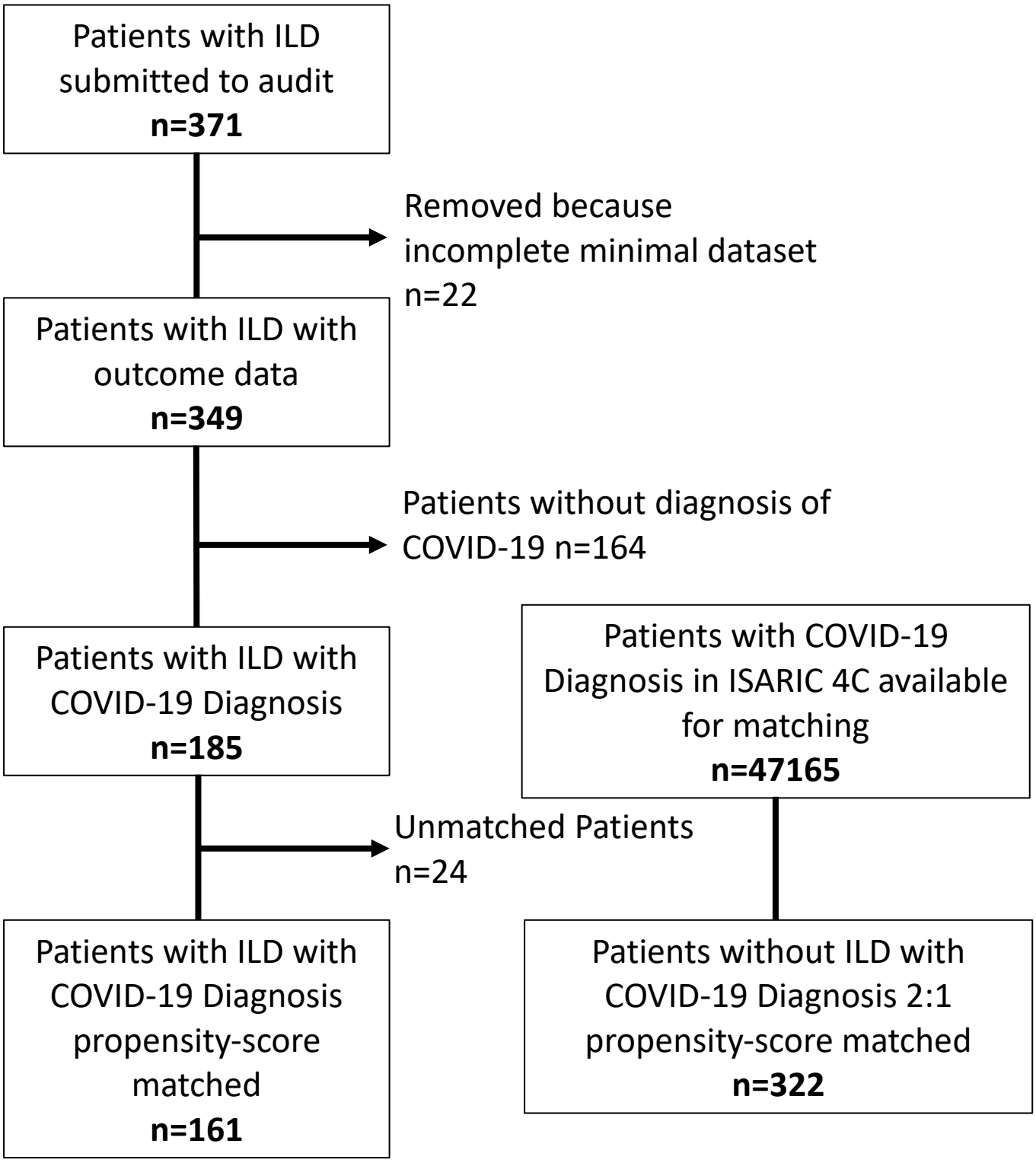

Figure 2 A) In Hospital Mortality with 95% confidence intervals for female ILD patients hospitalized with COVID-19 stratified by age compared with those without ILD. B) In Hospital Mortality with 95% confidence intervals for male ILD patients hospitalized with COVID-19 stratified by age compared with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

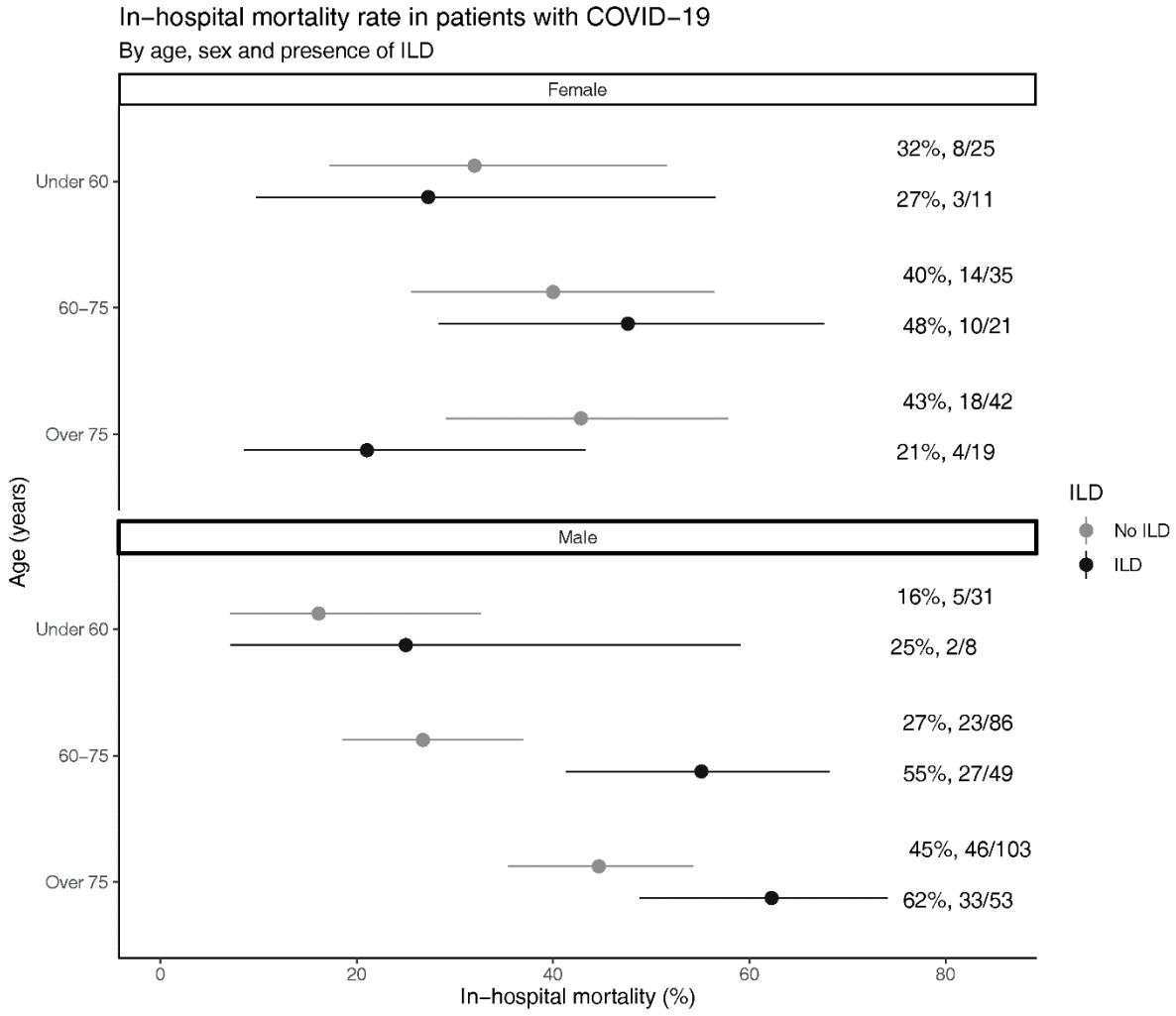

Figure 3 A) Effect of ILD on mortality following COVID-19 (Propensity Matched), B) effect of obesity and ILD (Propensity Matched) C) and effect of FVC on outcome in ILD patients only.

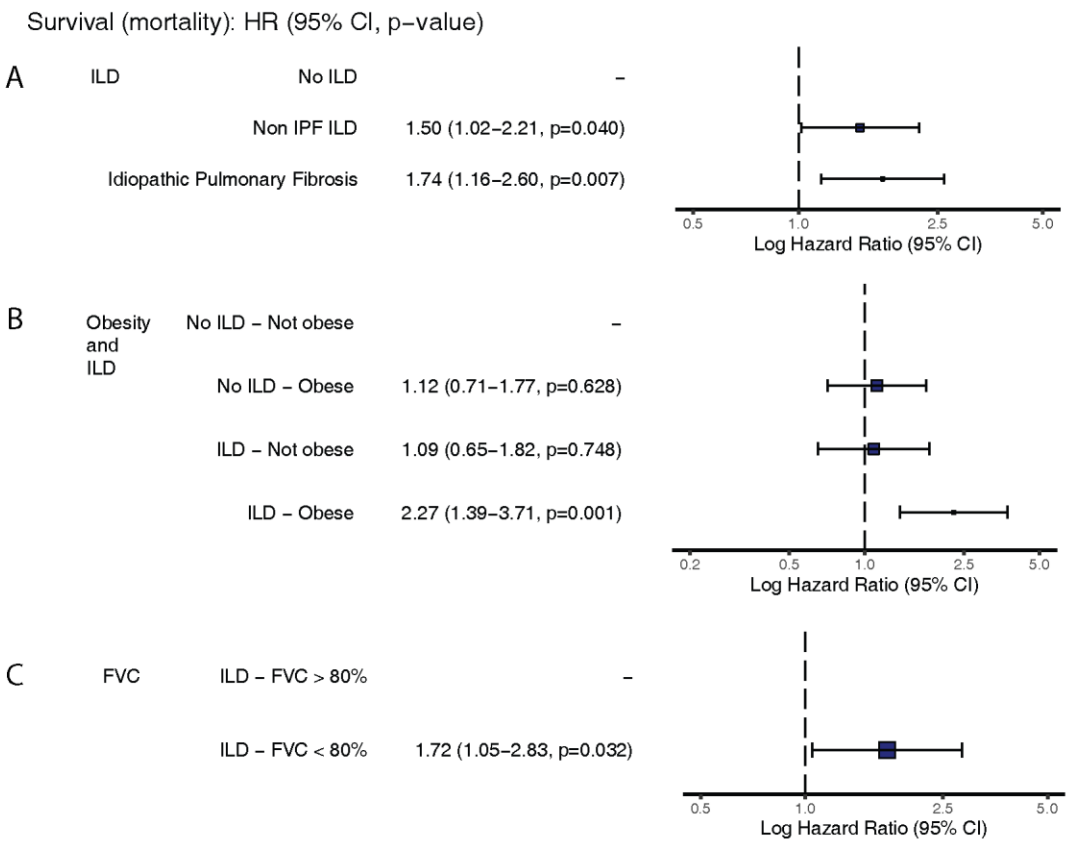

Table 1 – Patient Characteristics by ILD

	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 Hypersensitivity Pneumonitis	0 (0.0)	14 (8.7)	
		Connective Tissue Disease related ILD	0 (0.0)	13 (8.1)	
		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	23 (7.1)	45 (28.0)	<0.001
		(Missing)	32 (9.9)	32 (19.9)	
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 respiratory support*	254 (78.9)	136 (84.5)	0.288
		Enhanced Respiratory Support	39 (12.1)	20 (12.4)	
		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 O_2 considered enhanced respiratory support. **where Kruskall 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 Kruskall 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 O_2 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.

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Outcome of COVID-19 in patients hospitalized with Interstitial Lung Disease: An international multicenter study. Supplementary Material.

Supplementary Table 1

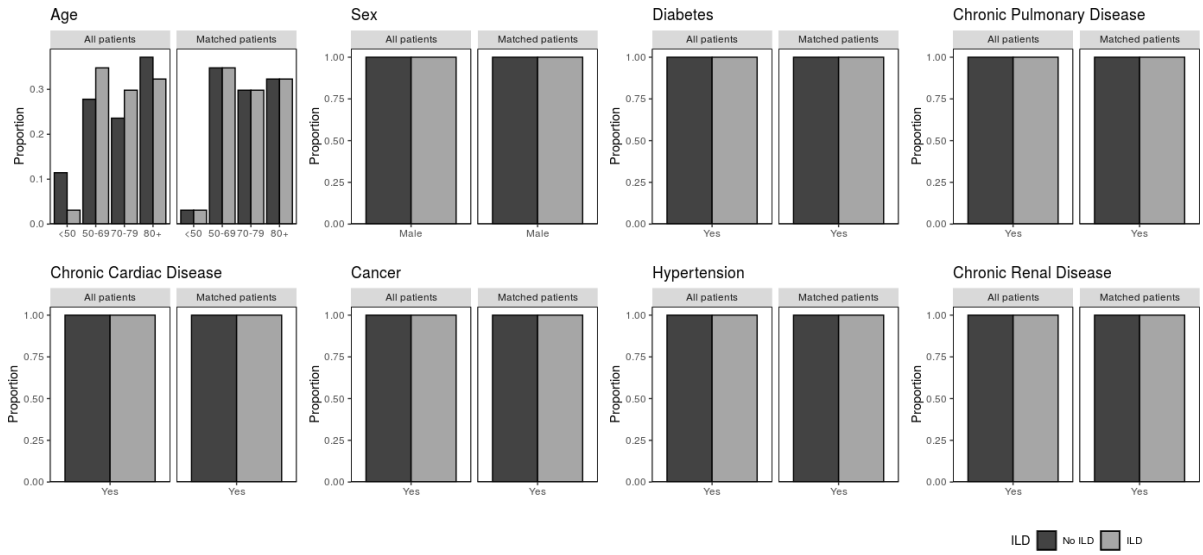
COUNTRY	NUMBER	PERCENTAGE
UK	299	86
REPUBLIC OF IRELAND	11	3
SPAIN	27	7.5
GERMAN	5	1.5
ITALY	5	1.5
DENMARK	<3	<1

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 Intestitial 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.



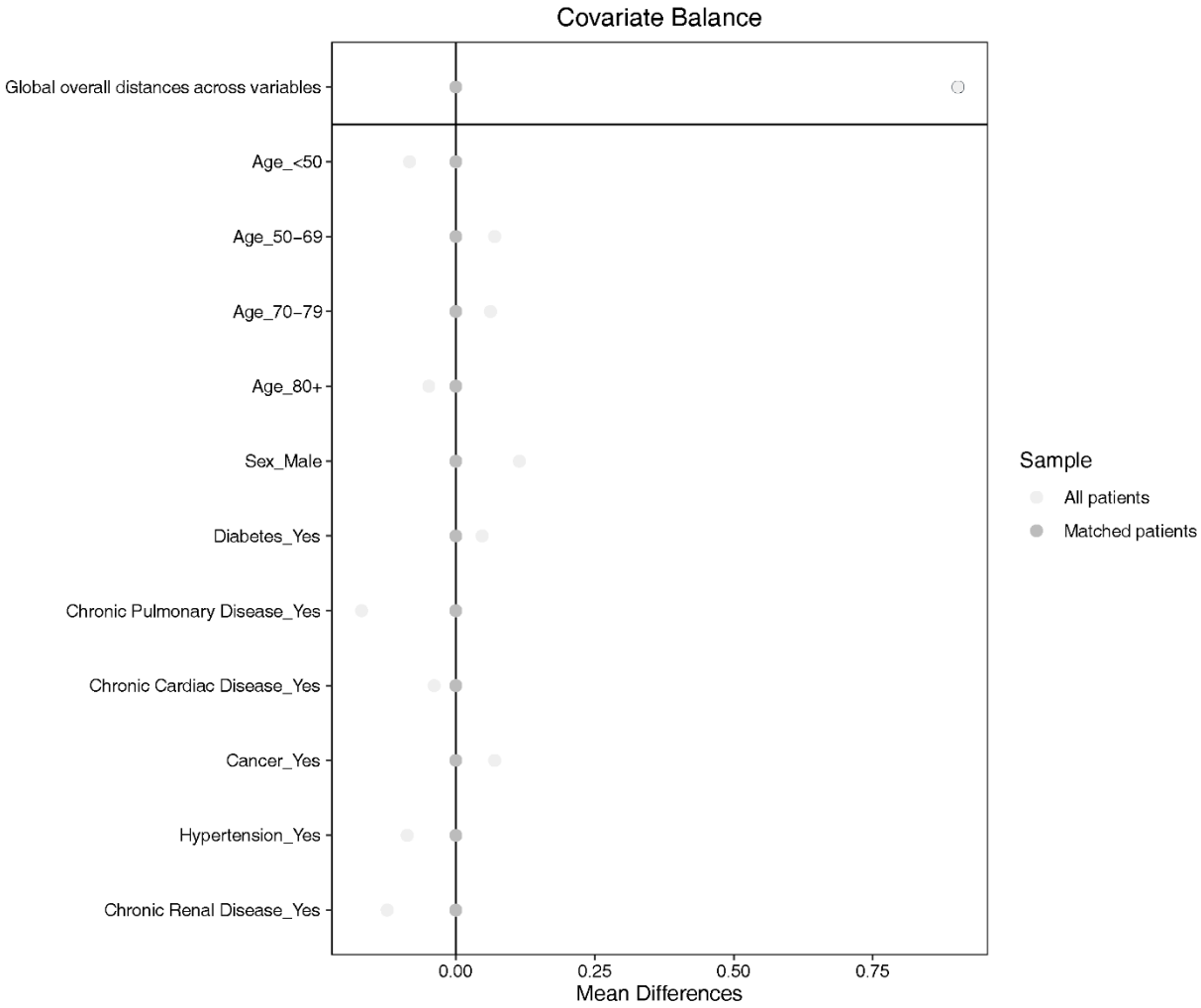


Figure S2 Impact of sex, and co-morbidity on outcomes of COVID-19 in ILD]

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)