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Original Research



Impact of interstitial lung disease on COVID-19 severity: A nationwide register study

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ABSTRACT

Aim: To investigate if ILD is associated with increased severity of COVID-19 and if this association differs by disease type or vaccination status.
Methods: Data from Swedish national registers within the SCIFI-PEARL study was used to examine the relationship between ILD and three levels of COVID-19 severity: non-hospitalized, hospitalized, and critical (ICU admission or death) from January 2020 to May 2022. We performed multinomial logistic regression, adjusted for confounding factors, and examined interactions with vaccination status.
Results: Altogether, 18,666 patients with ILD were included, comprising 8774 with fibrotic ILD and 9181 with sarcoidosis. Among ILD patients with COVID-19 (n = 3384), 18.9 % required hospitalization and 8.5 % had critical disease, compared to 3.8 % and 1.3 % respectively, among COVID-19 patients without ILD. ILD was associated with increased severity of COVID-19 compared to patients without ILD (Conditional Odds Ratio (COR) (95 % CI)): hospitalization 2.30 (2.09–2.54), critical disease 2.50 (2.17–2.88)). Corresponding CORs were 3.25 (2.81–3.75) and 3.46 (2.88–4.15) for fibrotic ILD, and 1.56 (1.34–1.81) and 1.57 (1.21–2.03) for sarcoidosis. Two or more vaccine doses protected against severe COVID-19 among patients with ILD and COVID-19, reducing hospitalizations (non-vaccinated: 21.8 %; vaccinated: 16.3 %), and an even stronger reduction in critical disease (non-vaccinated: 12.0 %; vaccinated: 3.6). However, even among fully vaccinated individuals, ILD remained significantly associated with increased severity of COVID-19.
Conclusions: ILD is associated with increased COVID-19 severity in patients with infection, particularly in patients with fibrotic ILD. Vaccination most effectively prevents critical illness. Our study underscores the continued importance of vaccination programs and preventive strategies.

1. Background

Individuals with reduced lung function and advanced pulmonary disease are susceptible to severe COVID-19 [1]. This includes patients with interstitial lung diseases (ILD), particularly idiopathic pulmonary fibrosis (IPF) [2–8]. Other commonly encountered risk factors for increased severity of COVID-19 include obesity, increased age, and comorbidities, which are common among ILD patients.

Pulmonary sarcoidosis, which often has a milder disease course compared to other ILDs [9,10], is not as well studied in relation to severe COVID-19. Previous studies have shown contradictory findings after adjusting for other known risk factors, and none have studied this association after vaccination [11–15].

The pathophysiological mechanisms underlying the elevated risk of severe COVID-19 in patients with ILD are still debated. However, they may relate to factors such as an underlying susceptibility to inflammatory triggers, the effects of pharmacotherapy for ILD, reduced lung function, and increased susceptibility to further respiratory impairment,

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or a combination of these factors [13,16–19].

After widespread vaccinations and the resolution of the pandemic, COVID-19 is no longer considered a public health emergency, as the risk for severe disease in healthy individuals has decreased significantly [20]. However, the elevated risk for severe COVID-19 associated with chronic lung diseases seems to persist [5–7,22–25]. Previous studies on the effects of vaccination on the risk of severe COVID-19 have not been adequately powered to address potential confounders and have not examined different types of ILD separately. Therefore, it is still unclear how effective the COVID-19 vaccinations are for patients with ILD and if the effectiveness differs from the general population.

Given these knowledge gaps, this study aimed to investigate if ILD is associated with increased severity of COVID-19 in individuals with the infection and, if so, how this association varies based on the type of ILD. A further aim was to examine to what degree vaccination attenuates the severity of COVID-19 in patients with ILD.

2. Study design and methods

2.1. Study design, population, and time periods

The Swedish Covid-19 Investigation for Future Insights - a Population Epidemiology Approach using Register Linkage (SCIFI-PEARL) project links demographic, health-related, and other register data for the entire Swedish population with data on COVID-19, as previously described [26]. We conducted a population-based cohort study nested within SCIFI-PEARL for the period from January 2020 to May 2022. An overview of the data sources detailed below is shown in Fig. 1.

2.2. Cohort source and definition of interstitial lung disease

The source population was the entire population aged 18 or older as of January 1, 2020 (index date), and this cohort was used to calculate the cumulative incidence of COVID-19 (Fig. 2). Having a pre-existing interstitial lung disease ("all ILD") was defined as having any of the following ICD-10 codes from 2015 to 01-01 until 2019-12-31 as a primary or secondary diagnosis from inpatient or specialist outpatient care in the Swedish National Patient Register (NPR): J84.0, J84.1, J84.8, J84.9, J99.0, J99.1, D86.0, D86.2, and D86.9 (Supplementary Table S1). We then defined two subgroups: "fibrotic ILD" (J84.1 and J84.9; i.e., capturing fibrotic ILD broadly) and "sarcoidosis" (D86.0, D86.2, and D86.9; i.e., capturing sarcoidosis with pulmonary involvement). The remaining population was classified as "no ILD."

Secondary subgroups within the "all ILD" group were defined as "Non-fibrotic ILD" (belonging to the all ILD group but not in the fibrotic ILD group), "Non-fibrotic sarcoidosis" (belonging to the sarcoidosis group but not in the fibrotic ILD group, and "other ILDs" (belonging to the all ILD group but not in the fibrotic ILD or sarcoidosis groups).

2.3. Definition of COVID-19 main cohort inclusion

The COVID-19 event date was defined as the earliest occurrence of any of the following: a laboratory-confirmed positive SARS-CoV-2 test, a specialist outpatient diagnosis, an inpatient diagnosis, or a cause of death, during the follow-up period from 2020 to 01-01 to 2022-05-31.

COVID-19 test data were obtained from the mandatory national database of notifiable communicable diseases, SmiNet. Data on hospitalizations and outpatient diagnoses in specialist care were acquired from the NPR. Data on treatment in ICU were obtained from the Swedish

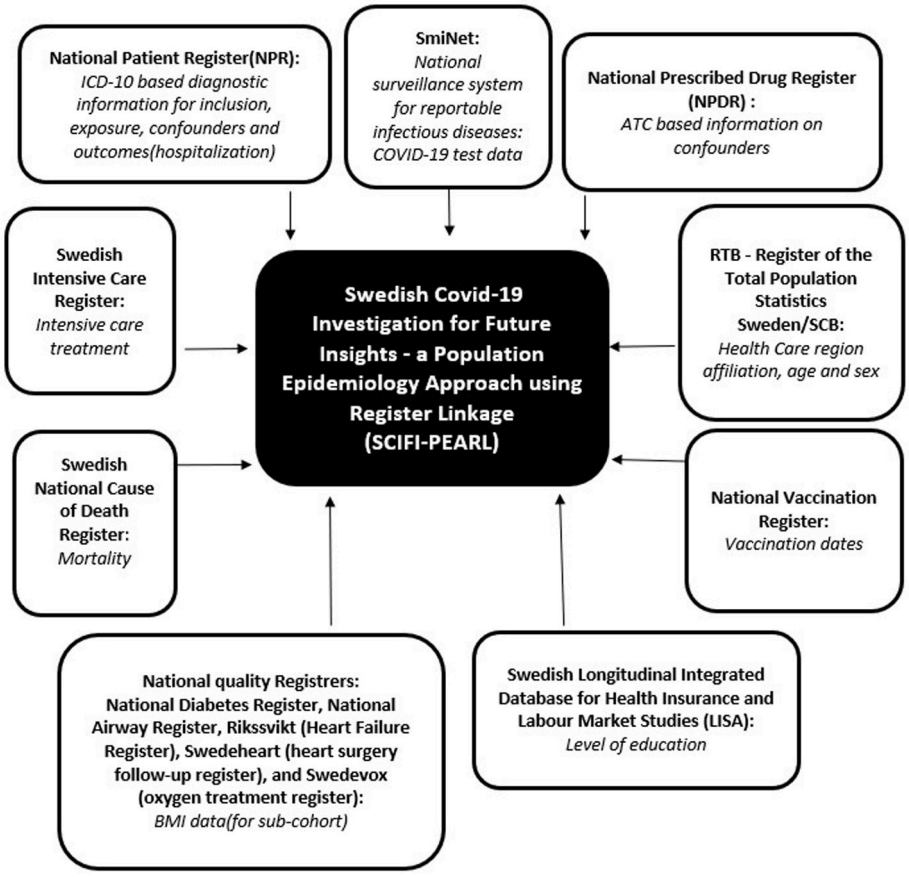

Fig. 1. Registers used as data sources
BMI= Body mass index, ICD-10 = International Classification of Disease Tenth Revision, ATC = Anatomic Therapeutic Chemical classification system.

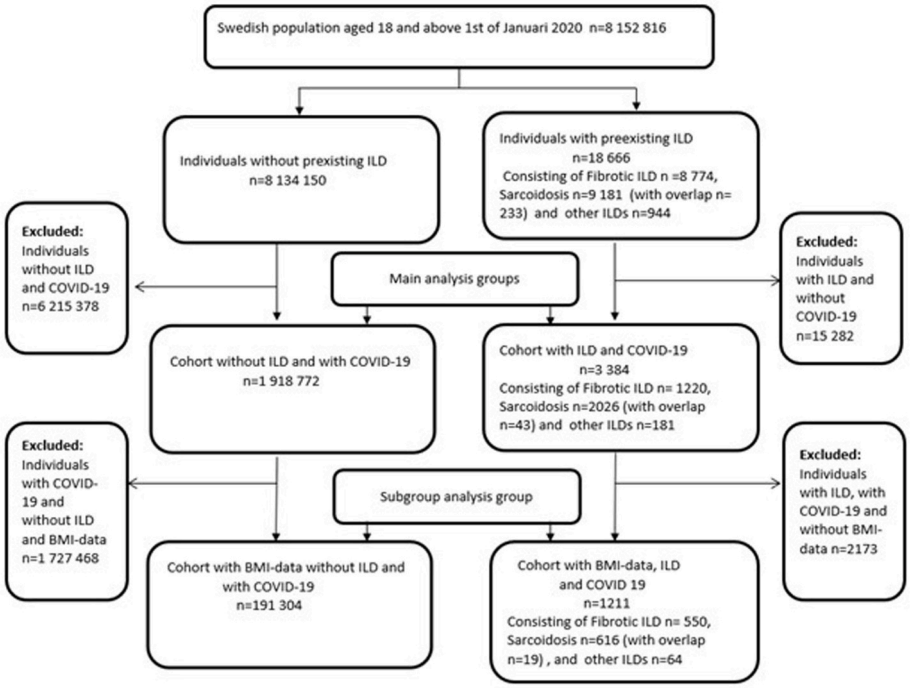

Fig. 2. Flow chart showing the studied population.
ILD=Interstitial Lung Disease, BMI= Body mass index, COVID-19 cases are those occurring between 2020 and 01-01 and 2022-05-31.

Intensive Care Register. Data on mortality was acquired from the Swedish National Cause of Death Register. Diagnosis codes used were U07.1 and U07.2, recorded as primary or secondary diagnoses, or as the underlying or contributing cause of death (Supplementary Table S1).

Patients with a defined COVID-19 event date were included in the cohort for the main analysis, which compared outcomes between patients with and without ILDs. A flowchart for inclusion, exclusion, and comparison of groups is shown in Fig. 2.

2.4. Definition of outcome measures

The severity of COVID-19 infection was categorized into three possible outcomes: 1) non-hospitalized, 2) requiring hospitalization, and 3) critical (requiring treatment in the intensive care unit (ICU), or death from COVID-19). Hospitalization, ICU admission, or death related to COVID-19 were assessed based on data from within 90 days of the infection event date. These outcomes were identified using the same sources as those used to detect the COVID-19-event. A COVID-19 event without related hospitalization or death was classified into the non-hospitalized group.

2.5. Confounders and sub-cohort inclusion

Other possible risk factors for severe COVID-19 before the index date (January 1, 2020) were assessed, including hypertension, ischemic heart disease, heart failure, renal disease, and treatment with medication for diabetes or inhaler medications for respiratory disease. These data were collected from the NPR 2015–2019 and the Swedish National Prescribed Drug Register (NPDR) 2018–2019, respectively (Supplementary Table S1) [27,28].

We also used the Swedish Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA; Statistics Sweden/SCB) to collect information on the highest level of education achieved from 2018 until the index date, categorizing it into: completed primary, secondary (generally 2–3 years of voluntary education beyond compulsory school), and tertiary education (university-level studies). Healthcare Region was defined based on the legal residence listed (Statistics Sweden/SCB) on the index date, with the country divided into six major Healthcare Regions. Age on index date and sex were also collected from the general population register (Statistics Sweden/SCB) [29].

Body mass index (BMI) categories were available for a sub-cohort based on registered measurements, along with data on obesity diagnoses or treatment from the NPR and NPDR. Additional data were also obtained from other national quality registers, including the National Diabetes Register, National Airway Register, Rikssvikt (Heart Failure Register), Swedeheart (heart surgery follow-up register), and Swedevox (oxygen treatment register). These measurements, treatments, or diagnoses was used to categorize BMI into four groups: BMI$<$18.5 kg/m^2, BMI 18.5–24.9 kg/m^2, BMI 25–29.9 kg/m^2, and BMI $\geq$ 30 kg/m^2 [26]. (Supplementary Table S1).

2.6. Vaccination

Vaccination data were obtained from the National Vaccination Register [30]. A separate analysis was performed with vaccination status defined according to the number of vaccine doses at the time of the COVID-19 event. Individuals who had received two or more doses, with the last dose administered $\leq$6 months before the onset of COVID-19 disease, were defined as “vaccinated(2+doses)". Individuals with fewer than two doses were classified as"single-dose/unvaccinated”. Individuals who received two or more doses, with the latest dose administered $>$6 months prior to COVID-19, were excluded from this analysis, as the effectiveness of the vaccine was deemed uncertain after that time [21].

2.7. COVID-19 wave definition

Whether an outcome belongs to a specific COVID-19 wave was defined according to the date of the COVID-19 event. Wave one covered the first pandemic phase, from March 2020 to January 2021; the second was from February 2021 to June 2021; and the third was the remainder of 2021 and continued until the end of 2022. These definitions are consistent with those used by the Swedish National Board of Health and

Welfare [31].

2.8. Statistical analysis

Statistical analysis was performed using STATA 18 (StataCorp, College Station, TX, U.S.A.), and statistical significance was defined as a two-sided p-value of <0.05. Figures were generated using Excel (version 2108) and R 4.4.2.

The cumulative incidence rate was calculated by dividing the number of registered cases by the entire group size, and differences between groups were assessed using the Chi-squared test. Associations between ILD status and COVID-19 severity were estimated using multinomial logistic regressions, both unadjusted and adjusted for confounders, to obtain Conditional Odds Ratios (COR) with 95 % confidence intervals (CI) [32]. The adjustment included sex, age, use of inhaler medication, ischemic heart disease, heart failure, chronic renal disease, diabetes, and healthcare region. The analysis was repeated after stratification by age (<60 and ≥ 60 years). The main analysis was also repeated for the secondary ILD subgroups. Different waves were compared using the main model, after adjusting for vaccination effect. In the sub-cohort with data on BMI, an additional model was adjusted for BMI categories.

2.9. Interaction analysis

Using a common reference category, the lowest-risk strata consisting of COVID-19 cases without ILD and with vaccination, comparisons were made with three other exposure strata: 1) cases without ILD and without vaccination; 2) cases with ILD and with vaccination; and 3) cases with ILD and without vaccination. The same adjusted multinomial regression model, as described above for the main analysis, was used to calculate COR with 95 % CI. These analyses were then used to assess deviations from additive and multiplicative interactions between ILD and vaccination, using the relative excess risk increase (RERI) and ratio of ratios methods, respectively [33]. In brief, a RERI above 0 indicates more than additive risk increase from the two factors studied (here, ILD and non-vaccination) with the group lacking both risk factors as reference group. RERI is calculated as follows:

$$RERI = OR_{\mathrm{ILD,non-vaccine}} - OR_{\mathrm{ILD,vaccine}} - OR_{\mathrm{non-ILD,non-vaccine}} + 1$$

Ratio of ratios is calculated as follows:

$$Ratio\ of\ ratios = \frac{OR_{\mathrm{ILD,non-vaccine}}}{OR_{\mathrm{ILD,vaccine}} * OR_{\mathrm{non-ILD,non-vaccine}}}$$

If the ratio of ratios for the interacting factors (here, ILD and non-vaccination) has a value below 1, it indicates a less than multiplicative interaction, while a value above 1 suggests a supra-multiplicative interaction. In both cases an effect above the limit indicates a greater combined effect in the presence of both risk factors than given by only the risk factors themselves, i.e. an interaction whereby they potentiate each other on this scale. The interaction analysis was also conducted stratified by age (<60 and ≥ 60 years).

2.10. Ethics

The SCIFI-PEARL study was approved by Swedish Ethical Review Authority (2020–01800 and subsequent amendments). Individual informed consent was waived due to the use of register data.

3. Results

3.1. Population characteristics and cumulative incidence of COVID-19

A comparison between patients with ILD and the general population is shown in Table 1, along with the number of patients belonging to the primary ILD groups, including 233 belonging to both the sarcoidosis and fibrotic subgroups. Patients with ILD, especially patients with fibrotic ILD, were, on average, older, more often male, had lower levels of education, and had more comorbidities. In the sub-cohort where BMI was available, individuals were significantly older, more often female, and had more comorbidities compared to individuals for whom BMI was lacking (Supplementary Table S2). The cumulative incidence of COVID-19 was significantly lower in all ILD groups compared to the general population, with the lowest incidence observed in the fibrotic ILD group (Table 2).

Table 1
Population characteristics of the adult population in Sweden as of January 1, 2020, for individuals with and without Interstitial Lung Disease (ILD), including subgroups of ILD.

		No ILD	All ILD	Fibrotic ILD	Sarcoidosis
Number of individuals[a]		N = 8,134,150	N = 18,666	N = 8774	N = 9181
Male Sex		50.0 %	56.2 %	55.7 %	58.3 %
Education level	Primary	17.7 %	24.6 %	31.2 %	18.3 %
	Secondary	44.2 %	46.5 %	44.3 %	49.0 %
	Tertiary	38.1 %	28.9 %	24.5 %	32.6 %
Mean Age (IQR)		48 (33–65)	68 (55–77)	75 (67–81)	58 (48–70)
Proportion >60 years		32.2 %	67.0 %	87.5 %	47.4 %
Comorbidities and medications					
Heart failure		1.7 %	12.2 %	18.1 %	6.6 %
Hypertension		9.6 %	35.3 %	44.0 %	27.0 %
Ischemic heart disease		3.1 %	13.7 %	20.2 %	7.6 %
Chronic kidney disease		0.3 %	2.2 %	2.6 %	1.8 %
Antidiabetic medication		6.1 %	16.5 %	18.7 %	14.7 %
Inhaler medication		8.5 %	34.3 %	38.3 %	31.3 %

[a] Overlap between Fibrotic ILD and Sarcoidosis: 233 individuals; ILD other than fibrotic or sarcoidosis: 944 individuals (non-fibrotic, non-sarcoidosis).

3.2. Severity of COVID-19 in patients with infection

The three main ILD groups had a higher proportion of severe COVID-19 outcomes than the non-ILD general population, as well as higher conditional odds ratios (Table 2).

After adjustments for confounding factors, elevated CORs remained for all ILD groups, albeit with lower estimates. This was most apparent for fibrotic ILD but was also evident in the other groups and remained unchanged after stratification by age (<60 and ≥ 60 years) (Fig. 3, Supplementary Fig. S1). In the sub-cohort with available BMI values, the findings remained largely unchanged after an additional adjustment for BMI, albeit with wider confidence intervals (Fig. 3).

Regarding the secondary ILD subgroups, the CORs for the non-fibrotic ILD group and the non-fibrotic sarcoidosis ILD group were equivalent to that of the sarcoidosis group, and lower than for the "all ILD" group. In contrast, the COR for the "other ILD" group (non-fibrotic non-sarcoidosis) was similar to or greater than that of the fibrotic ILD group (Supplementary Fig. S1). During the different pandemic waves, the CORs for COVID-19 severity related to ILD increased from the first to the last wave (Supplementary Fig. S2).

3.3. Vaccination effects and interaction with ILD in patients with infection

There was a strong and significant reduction in the proportion of patients with ILD experiencing critical illness after completing the two dose vaccination course within 6 months of illness, i.e. being fully vaccinated. However, the reduction in hospitalization rates was smaller, especially among patients with fibrotic ILD (Table 2).

In the interaction analysis of vaccination status and ILD, belonging to the "single-dose/unvaccinated" group (with most of this group being completely unvaccinated) and having ILD were both associated with increased severity of COVID-19. This association was strongest in fibrotic ILD. The RERI and ratio of ratios indicated that all interactions

Table 2
Cumulative Incidence and proportion of individuals with COVID-19 from January 2020 to May 2022 among the adult population in Sweden and proportions with two levels of severe COVID-19, with and without Interstitial Lung Disease (ILD) and by ILD subgroup, and stratified by vaccination status, with unadjusted Conditional Odds ratio (COR) comparing to those without ILD and the same vaccination status.

	Outcome	No ILD	All ILD	Fibrotic ILD	Sarcoidosis
Cumulative Incidence of COVID-19 in the source population, % (N)	All Covid-19	23.6 % (1,918,772)	18.1 % (3384)	13.9 % (1220)	22.1 % (2026)
Severity of COVID-19 (proportion among COVID-19 cases), % (N) Unadjusted COR (95 %CI)					
ALL					
	Hospitalization	3.8 % (73,442)	18.9 % (640)	31.7 % (387)	10.9 %(220)
		1 (Ref)	6.46 (5.92–7.04)	15.2 (13.42–17.29)	3.12 (2.71–3.60)
	Critical[a]	1.3 % (25,124)	8.5 % (287)	16.8 % (205)	3.5 % (70)
		1 (Ref)	8.46 (7.48–9.57)	23.60 (20.14–27.64)	2.90 (2.28–3.68)
STRATIFIED ANALYSIS					
Single-dose/unvaccinated[b] (count shown separately followed by total)	Hospitalization	5.3 % (2639/55,213/57,852)	21.8 % (32/381/413)	33.5 % (23/212/235)	13.5 % (7/146/153)
		1 (Ref)	5.77 (5.16–6.45)	13.59 (11.46–16.12)	2.91 (2.45–3.45)
	Critical[a]	2.0 % (1049/20,933/21,982)	12.0 % (14/214/228)	23.3 % (8/155/163)	4.9 % (6/49/55)
		1 (Ref)	8.38 (7.27–9.65)	25.57 (21.17–30.89)	2.75 (2.10–3.61)
Vaccinated(2+ doses)[b]	Hospitalization	1.8 % (15590)	16.3 % (227)	30.1 % (152)	8.2 % (67)
		1 (Ref)	11.02 (9.5–12.72)	25.74 (21.23–31.21)	4.96 (3.86–6.37)
	Critical[a]	0.35 % (3142)	3.6 % (59)	6.9 % (42)	1.6 % (15)
		1 (Ref)	14.21 (10.92–18.51)	35.29 (25.55–48.75)	5.51 (3.30–9.20)

Data are presented as percentages of the total, with the number of cases in brackets, divided into subgroups where applicable(single dose/no dose/total).
[a] ICU admission or death.
[b] At time of Covid-19 infection. Vaccinated (2+ doses) was defined as having received two or more doses of the COVID-19 vaccine, with the latest within 6 months of contracting COVID-19. Single-dose/unvaccinated was defined as having received fewer than two doses at time of Covid-19 infection. The analysis excluded individuals who had received two doses but where the last dose was more than 6 months before contracting COVID-19.

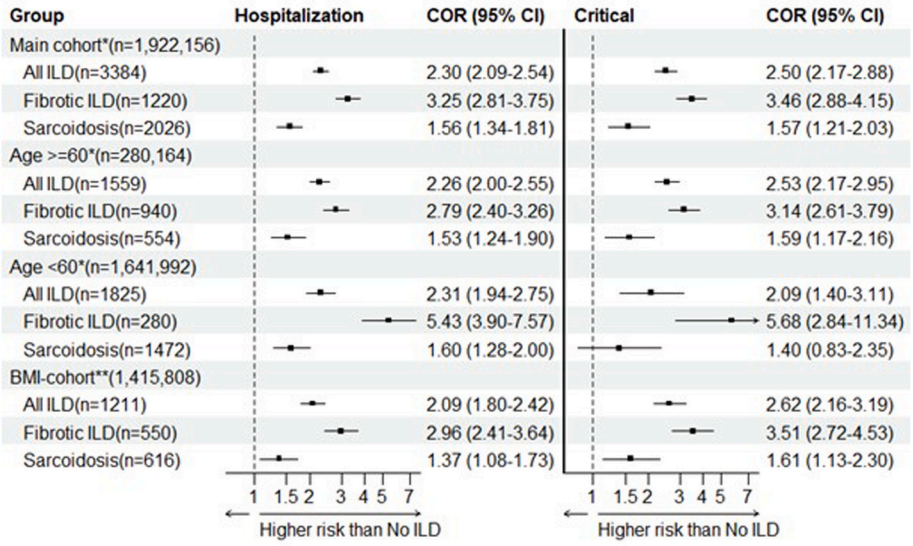

Fig. 3. Adjusted* conditional odds ratios (COR) with 95 % confidence intervals (CI) for increased severity of COVID-19 (hospitalization and critical disease) for those with infection in Sweden from January 2020 to May 2022, relative to non-hospitalized COVID-19 cases. The analysis compares COVID-19 cases with underlying Interstitial Lung Disease (ILD) with COVID-19 cases without ILD, overall and by ILD subgroup, for the whole main cohort, stratified for age (<60 and ≥ 60 years), and for the BMI sub-cohort.
Total number of COVID-19 cases for each group and cohort listed in parenthesis after name of group or cohort. Critical disease includes those with ICU admission or death. * = adjusted for sex, age, healthcare region, ischemic heart disease, heart failure, chronic renal disease, diabetic and inhaled medication. ** = adjusted for sex, age, healthcare region, ischemic heart disease, heart failure, chronic renal disease, diabetic and inhaled medication, as well as BMI-status.

were supra-additive but less than multiplicative. However, the deviation from additivity did not reach statistical significance in the analyses by type of ILD due to smaller sample sizes (Table 3).

The same analysis was repeated after stratification by age (<60 and ≥ 60 years), with similar results (Supplementary Table S3).

Table 3
Adjusted[a] conditional odds ratios (COR) with 95 % confidence intervals (CI) for increased severity of COVID-19 (hospitalization and critical disease) for those with infection in Sweden from January 2020 to May 2022, relative to non-hospitalized COVID-19 cases. The analysis compares Interstitial Lung Disease (ILD) status and vaccination status to a common reference category of no ILD and having completed 2-dose vaccination course, showing the Relative Excessive Risk Increase (RERI) and the ratio of ratios.

All ILD					
	Hospitalization		1	**Critical**[b]	
COR(95 %CI)	**No ILD**	**ILD**		**No ILD**	**ILD**
Vaccinated(2+ doses)	1(reference)	3.29(2.80–3.86)		1(reference)	3.81(2.86–5.08)
Single-dose/unvaccinated	3.50(3.43–3.57)	7.20(6.33–8.18)		8.07(7.75–8.40)	19.43(16.35–23.08)
	RERI[c]	**Ratio of Ratios**[c,a]		**RERI**[c]	**Ratio of Ratios**[c,a]
	1.42(0.36–2.47)	0.63(0.50–0.75)		8.55(5.09–12.01)	0.63(0.42–0.84)
Fibrotic ILD					
	Hospitalization			**Critical**[b]	
COR(95 %CI)	**No ILD**	**Fibrotic ILD**		**No ILD**	**Fibrotic ILD**
Vaccinated(2+ doses)	1(reference)	5.19(4.17–6.45)		reference	5.49(3.86–7.82)
Single-dose/unvaccinated	3.49(3.42–3.56)	9.33(7.67–11.33)		8.05(7.73–8.38)	25.48(20.27–32.03)
	RERI[c]	**Ratio of Ratios**[c,a]		**RERI**[c]	**Ratio of Ratios**[c,a]
	1.64(-0.49–3.77)	0.51(0.36–0.66)		12.93(6.85–19.02)	0.58(0.33–0.82)
Sarcoidosis					
	Hospitalization			**Critical**[b]	
COR(95 %CI)	**No ILD**	**Sarcoidosis**		**No ILD**	**Sarcoidosis**
Vaccinated(2+ doses)	1(reference)	1.89(1.44–2.48)		1(reference)	2.32(1.33–4.03)
Single-dose/unvaccinated	3.48(3.41–3.55)	5.24(4.34–6.31)		8.03(7.71–8.35)	12.74(9.41–17.26)
	RERI[c]	**Ratio of Ratios**[c,a]		**RER**[c]	**Ratio of Ratios**[c,a]
	0.86(-0.24–1.96)	0.80(0.53–1.06)		3.39(-0.64–7.45)	0.69(0.25–1.12)

$$Ratio\ of\ ratios = \frac{OR_{\mathrm{ILD,non-vaccine}}}{OR_{\mathrm{ILD,vaccine}} * OR_{\mathrm{non-ILD,non-vaccine}}}$$

[a] Adjusted for sex, age, healthcare region, ischemic heart disease, heart failure, chronic renal disease, diabetic and inhaled medication.
[b] ICU admission or death.
[c] $RERI = OR_{\mathrm{ILD,non-vaccine}} - OR_{\mathrm{ILD,vaccine}} - OR_{\mathrm{non-ILD,non-vaccine}} + 1$

4. Discussion

In this nationwide study, we found that ILD, particularly fibrotic ILD, was strongly associated with increased severity of COVID-19 among individuals with the infection. The odds ratio for both hospitalization and critical illness in ILD patients was more than doubled, and for fibrotic ILD tripled, compared to the general population. We also found that sarcoidosis was associated with increased severity of COVID-19, independent of various confounding factors, including BMI. The reduction in the odds ratio of critical disease induced by vaccination was lower among individuals with ILD compared to those without ILD. Still, vaccination reduced the proportion of critical COVID-19 cases among patients with ILD more than among individuals without ILD.

The lower cumulative incidence of COVID-19 overall (mild and severe disease combined) in individuals with ILD compared to the general population may be explained by heightened risk awareness. Official recommendations, related to age and underlying disease, encouraged avoidance of exposure. In the sarcoidosis subgroup, the cumulative incidence was also significantly lower, but not to the same degree as in the main ILD group. This may reflect the younger average age in this group, meaning they were less frequently included in age-defined risk groups. Furthermore, individuals with sarcoidosis, unlike patients with other ILDs, were not classified as a risk group unless their lung function was significantly decreased. However, similar to other ILD patients, patients with sarcoidosis who contracted COVID-19 experienced more severe outcomes.

The association between ILD and severe COVID-19 has been previously described [2–8,22], but the strength of this association has varied depending on the different outcome measures used. None of the previous studies have been based on a nationwide cohort of a similar size with a multilevel outcome of COVID-19 or have considered vaccination effects. This study, thus, provides the most comprehensive evaluation of this relationship and offers the most reliable quantification.

As BMI data were mostly collected from registers for chronic diseases, requiring the presence of comorbidities, these individuals were generally older and had more underlying health conditions. However, the effects of ILD remained consistent in the sub-cohort with available BMI data, even after adjusting for BMI.

Our finding that sarcoidosis is associated with increased severity of COVID-19 contrasts with some previous studies [11,12], but is in agreement with at least one other [14], perhaps related to small sample sizes. A review found that the increased risk was most likely linked to comorbidities and, possibly, immunosuppressant use [15]. However, in our study, the association remained after adjusting for comorbidities. A previous study in Sweden reported a relatively low (<20 %) frequency of systemic immunosuppressant use predisposing to infection [34] among patients with sarcoidosis. Given the previously shown effect of immunosuppressants on COVID-19 mortality in the Swedish population, this is unlikely to explain the association shown here [35]. A possible pathophysiological rationale for the increased risk in the sarcoidosis group is the involvement of the ACE signaling pathway and the concurrent activation of inflammatory signal pathways [13]. Previous Swedish studies comparing patients with sarcoidosis to the general population before the emergence of COVID-19 have shown increased mortality, especially among patients treated with immunosuppressants [36], as well as an increased rate of infections, including pneumonia [34].

The substantial reduction in the proportion of critical outcomes following vaccination, while the rate of hospitalization remains high, is in accordance with the clinical observation that viral infections pose little threat to healthier individuals but represent a major health risk for patients with underlying diseases such as ILD. The greater impact of vaccination on preventing critical disease compared to hospitalization may be explained by a downward shift in severity of COVID-19, i.e., patients who, if not fully vaccinated, would have developed critical disease may only require hospitalization after vaccination.

The interaction analysis shows an effect that is intermediate between additive and multiplicative, i.e., supra-additive but sub-multiplicative. This pattern is most clearly seen in the total group and the fibrotic ILD group for critical disease, with a consistent pattern observed for

hospitalization and sarcoidosis. Since the initial odds ratios are considerably higher for the ILD groups, even a stronger absolute reduction in severity of COVID-19 results in a weaker proportional effect [37]. This finding remains unchanged after stratifying by age (</≥60), showing that age-related decrease in vaccine effectiveness is unlikely to explain the difference between individuals with and without ILD. In summary, vaccination against COVID-19 provides substantial benefits for individuals with ILD, arguably greater than for individuals without ILD, offering strong protection primarily against critical COVID-19 generally. Nonetheless, even after vaccination, ILD patients remain at a significantly higher risk of severe COVID-19 when infected, especially hospitalization.

4.1. Strengths and limitations

This study has several strengths. Specifically, no other study has examined the severity of COVID-19 infection among ILD patients in a population of this size or over such a long period. The rich dataset, which allows for a comprehensive adjustment for comorbidities and other risk factors, also enhances the robustness of our findings.

However, this study has some limitations. There is uncertainty about exact diagnoses, since the same ICD-10 codes can include several clinically distinct variants of ILD. The study covers the active testing period for COVID-19 in Sweden, but variations in testing availability and strategies during the pandemic, especially during the first wave, mean that the cumulative incidence data should be interpreted with caution. Moreover, the dataset did not include information on lung function or immunosuppressive medication. The lack of information on smoking status may be partially mitigated by its correlation with the included sociodemographic variable of education level.

5. Conclusion

ILD was strongly associated with increased severity of COVID-19 in patients with infection. The odds ratios were more than twice as high for patients with ILD and more than three times as high for patients with fibrotic ILD compared to individuals without ILD. Although vaccination clearly reduced the severity of COVID-19 among ILD-patients, especially against critical disease (death or ICU-treatment), ILD remained strongly associated with increased severity even among vaccinated individuals. This reaffirms that there is still a need for vaccination, clinical vigilance, and preventive strategies for these patient groups. The evidence that sarcoidosis was associated with a 50 % increase in both hospitalizations and critical COVID-19 implies that patients with sarcoidosis should be included in vaccination recommendations and preventive strategies for COVID-19. Additionally, they may need to be better targeted for protection against respiratory infections in general.

CRediT authorship contribution statement

Emil Ekbom: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Andrei Malinovschi:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Christer Janson:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Lisa Carlson:** Writing – review & editing, Conceptualization. **Magnus Sköld:** Writing – review & editing, Methodology, Conceptualization. **Huiqi Li:** Writing – review & editing, Software, Methodology, Data curation, Conceptualization. **Fredrik Nyberg:** Writing – review & editing, Resources, Methodology, Funding acquisition, Conceptualization. **Össur Ingi Emilsson:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: FN reports a relationship with AstraZeneca Pharmaceuticals LP that includes: equity or stocks. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2025.108372.

Glossary:

ATC	Anatomical Therapeutic Chemical classification system
BMI	Body mass index
CI	Confidence Interval
COR	Conditional Odds Ratios
COVID-19	Coronavirus Disease 2019
ICD-10	International Classification of Disease Tenth Revision
ICU	Intensive Care Unit
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
NPR	Swedish National Patient Register
NPDR	Swedish National Prescribed Drug Register
RERI	Relative Excess Risk Increase
SARS-CoV-2:	Severe Acute Respiratory Syndrome Coronavirus 2
SCIFI-PEARL:	Swedish Covid-19 Investigation for Future Insights - a Population Epidemiology Approach using Register Linkage

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