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Original Research

Risk and outcomes of COVID-19 in patients with oxygen-dependent chronic respiratory failure– a national cohort study

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ABSTRACT

Background: We aimed to evaluate cumulative occurrence and impact of COVID-19 in patients with chronic respiratory failure (CRF) treated with long-term oxygen therapy (LTOT).

Material and methods: Data were obtained from the SCIFI-PEARL study on the entire Swedish population and on patients with oxygen-dependent CRF and no COVID-19 diagnosis before start of LTOT. Analyses were performed for three time periods; pre-alpha (Jan–Dec 2020), alpha (Jan–Mar 2021) and delta/omicron (Apr 2021–May 2022). Cumulative incidence of laboratory-verified COVID-19 was compared between patients with CRF and the general population. Risk factors for severe (hospitalised) to critical (intensive care, or death ≤30 days after infection) COVID-19, and the impact of COVID-19 on one-year mortality, were analysed using multivariable Cox regression.

Results: Cumulative incidence of COVID-19 was higher in patients with CRF than in the general population during the pre-alpha period (6.4%/4.9%, $p = 0.002$), but less common during the alpha and delta/omicron periods (2.9%/3.8% and 7.8%/15.5%, $p < 0.0001$ for both). The risk of severe/critical COVID-19 was much higher in CRF patients during all periods (4.9%/0.5%, 3.8%/0.2% and 15.5%/0.5%, $p < 0.0001$ for all). Risk factors for COVID-19 infection in people with CRF were higher age, cardiovascular and renal disease, and COVID-19 was associated with increased one-year mortality following infection in the pre-alpha (HR 1.79; [95% CI] 1.27–2.53) and alpha periods (1.43; 1.03–1.99).

Conclusion: Patients with CRF had higher risk of severe/critical COVID-19 than the general population. COVID-19 infection was associated with excess one-year mortality.

1. Background

Since the start of the Coronavirus Disease 2019 (COVID-19) pandemic, over 758 million people have been confirmed diagnosed with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) worldwide [1]. By the end of February 2023, 2,698,535 cases of COVID-19 confirmed by PCR test had been reported by the Swedish Public Health Authority [2].

Several studies have reported that chronic respiratory diseases, in particular chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), are important risk factors for increased risk of hospitalisation and mortality in COVID-19 [3–6]. However, the evidence on patients with chronic respiratory diseases at risk for SARS CoV-2 infection is still contradictory [7,8].

A specific group of vulnerable patients with chronic respiratory disease are those with chronic respiratory failure (CRF) treated with long-term oxygen therapy (LTOT). We have previously reported that the risk of developing oxygen-dependent CRF *after* COVID-19 in a national

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cohort study was very low, but increased in patients with chronic respiratory diseases with no previous LTOT [9]. However, no study has explored the risk of incident COVID-19 in patients with ongoing LTOT, or if COVID-19 is associated with poor outcomes in LTOT patients. The Swedish National Registry of Respiratory Failure (Swedevox) includes about 85% of all patients starting LTOT in Sweden with high validity against medical records, offering a unique opportunity to address this research question in patients with CRF in need of oxygen supply [10,11]. As patients with CRF have a poor prognosis and consume large health-economic resources, it is of clinical interest for appropriate patient management to investigate if the risk of COVID-19 is increased compared with the general population and whether a COVID-19 infection in this patient group is associated with excess mortality.

The primary aim of this study was to investigate the risk of being diagnosed with COVID-19 infection in patients with oxygen-dependent CRF compared with the general population during different periods of the pandemic. Secondary aims included identification of risk factors for severe or critical COVID-19, and the impact of COVID-19 on one year-mortality in patients with oxygen-dependent CRF stratified for the different periods of the pandemic.

2. Methods

2.1. Study design, population and time periods

This was a population-based analysis of the nationwide Swedish Covid-19 Investigation for Future Insights - A Population Epidemiology Approach Using Register Linkage (SCIFI-PEARL) study, described in detail elsewhere [12], which includes demographic, health-related and other linked register data from all individuals in the Swedish population, including people with identified COVID-19.

The current study included CRF patients aged 18 years or older with ongoing LTOT, without any COVID-19 diagnosis before the start of LTOT. LTOT in Sweden is prescribed according to the BTS criteria [13] to non-smoking patients with a partial pressure of arterial oxygen (PO2) of <7.4 kPa (corresponding to 55 mmHg) breathing air, or PO_2 7.4−8.0 kPa (56–59 mmHg) with concomitant signs of right-sided heart failure, pulmonary hypertension, or secondary polycythemia, if the hypoxemia is persisting despite optimal therapy for the underlying disease. These criteria did not change during the pandemic.

A COVID-19 infection was defined as a first infection of laboratory-confirmed SARS-CoV-2 and thus the first case of each individual was included. The total study period from January 1, 2020 until May 31, 2022 was divided into several sub-periods based on dominant virus variants of concern: A) The “pre-alpha period” (January 1, 2020 to December 31, 2020) including the first wave and establishment of standard treatment, B) the “alpha period” (January 1, 2021 until March 31, 2021) with alpha variant dominance and introduction of mass vaccination in medical risk groups, and C) the “delta/omicron period” (April 1, 2021 until study end in May 31, 2022) which included the delta variant dominance and the first six months of the omicron variant dominance together with fully established mass vaccination in the country. For mortality analyses, one-year mortality risk was assessed after infections occurring during the pre-alpha period (one year from January 1, 2020), and after the alpha period (one year from April 1, 2021), for adequate follow-up time. For schematic overview, see Fig. 1.

For comparison, the incidence analysis of COVID-19 was repeated in general population, defined as the total Swedish population aged 18 years and above in January 1, 2020.

2.2. Variables

Data on COVID-19 morbidity and mortality were obtained from SmiNet, the mandatory national database of notifiable infectious diseases (positive tests), the Swedish National Patient Registry (comorbid conditions based on specialist care and COVID-19 hospitalisations), Swedish Intensive Care Register (ICU admissions) and the Swedish National Cause of Death Registry (mortality data) [2,12,14,15].

Severity of laboratory-confirmed COVID-19 disease was defined as mild (no hospitalisation), severe (hospitalised at common ward outside the intensive care unit (ICU)), and critical (admitted to ICU or fatal within one month of laboratory confirmation). A hospitalisation was defined as a test-positive hospitalisation, i.e. a COVID-19 case registered in the Patient Register as a hospitalisation with primary or secondary diagnosis coded with International Classification of Disease (ICD)-10 code U07.1 or U07.2, restricted to those who were test positive at an earlier date ≤45 days prior to hospitalisation or within 15 days of hospitalisation. The interval was chosen to include both accelerating symptoms causing hospitalisation in a later phase of an COVID-19-infection (soon after a positive test), and hospitalisations due to symptoms where COVID-19 was tested during the period of hospital care. Fatal COVID-19 was defined as death due to any cause within 30 days after laboratory-confirmed COVID-19. The general criteria for hospitalisation in Sweden were not changed during the pandemic.

Data on LTOT were obtained from Swedevox [10,11]. At start of LTOT, underlying primary cause for oxygen-dependent respiratory failure is registered. The causes were categorised as airway diseases (including COPD and emphysema without obstructive lung function impairment), parenchymal diseases (including idiopathic pulmonary fibrosis), cardiovascular diseases (including heart failure and pulmonary embolism), and other diseases (including unclear lung diseases and conditions with hypoventilation).

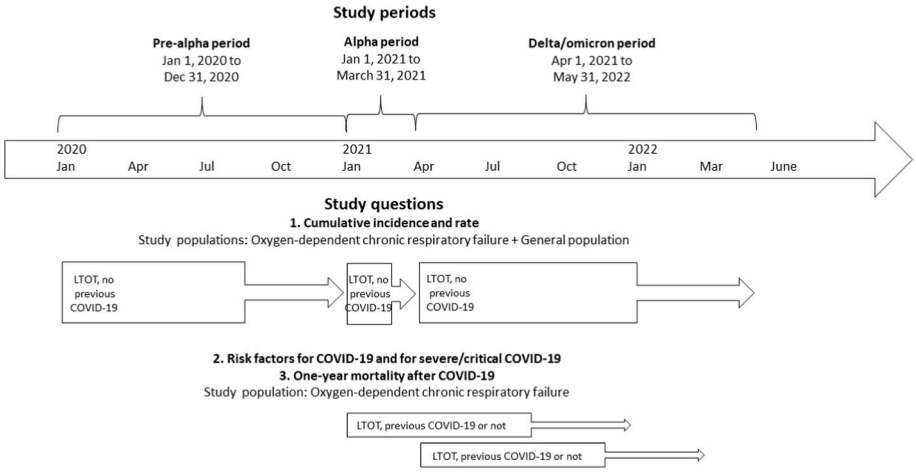

Fig. 1. Flow chart for study periods, study questions and study populations. *Abbreviations: COVID-19 = corona virus disease 2019, LTOT = long term oxygen therapy.*

Data on sex, age and educational level were derived from the Statistics Sweden LISA (Swedish Longitudinal Integrated Database for Health Insurance and Labour Market Studies) database [16]. Age was categorised as ≤ 70, 71–75, 76–80 and ≥ 81 years. Level of education was categorised as completing primary, secondary (generally 2–3 years of voluntary education beyond compulsory school), and tertiary education (university level studies).

Data on comorbidity risk groups according to the National Board of Health and Welfare [17] were obtained from the Swedish Patient Register based on specialist inpatient or outpatient care during 2015–2019 [17] and included chronic cardiovascular, lung, and renal disease, type 2 diabetes with complications, obesity, and hypertension. Chronic lung diseases included COPD (85%), interstitial lung disease, cystic fibrosis, or chronic respiratory failure from other causes.

2.3. Statistical analyses

Baseline characteristics of CRF patients at the start of each time period of dominating viral variant (pre-alpha, alpha, and delta/omicron) were compared between those with and without a laboratory-confirmed COVID-19 infection during respective period, using cross-tabulation.

Distribution of disease severity, cumulative incidence and rates of any COVID-19 infection and severe/critical COVID-19 infection were calculated separately for all three time periods. Cumulative incidence was defined as proportion of number of cases during each period in relation to all patients with ongoing LTOT but with no previous COVID-19 infection at the start of respective period. Rates were calculated as number of cases per 1000 person years in the investigated period. Corresponding analyses of disease severity, cumulative incidence and rates were also performed in the general population, with all adult people alive and with no previous COVID-19 infection at the start of each period, and compared with the CRF populations using cross-tabulation and Chi-2 test.

In patients with oxygen-dependent CRF, Cox regression with sex, age, level of education and comorbid conditions as independent variables was used to analyse time to COVID-19 and, respectively, to severe/critical COVID-19 within the three time periods, with censoring at death or last day in each period. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated.

The association of a first COVID-19 infection in the previous period with one-year mortality was analysed separately in all patients with ongoing LTOT on January 1, 2021 (after the pre-alpha period), and April 1, 2021 (after the alpha period), respectively. Cox regression with a first COVID-19 infection as independent variable and with adjustment for sex, age, level of education and comorbid conditions was used to analyse time to death within one year, with censoring at the first event of incident first laboratory-confirmed COVID-19 infection, death or at last day in each period.

Analyses were performed using IBM SPSS version 26 (IBM Corporation, Armonk, NY, USA), and statistical significance was defined as a two-sided $p < 0.05$.

2.4. Ethical considerations

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

3. Results

3.1. Patient characteristics

The total number of patients with ongoing LTOT and no previous COVID-19 was 1771 at the start of the pre-alpha period (January 1, 2020); 1649 at the start of the alpha period (January 1, 2021); and 1610 at the start of the delta/omicron period (April 1, 2021). Overall, a minority of all patients were men (pre-alpha period 35.9%, alpha period 36.6% and delta/omicron period 36.1%) and mean age (SD) was 76.1 (9.3), 75.1 (9.3) and 74.9 (9.32) years in the corresponding periods. The most common underlying cause of LTOT was airway disease (Table 1).

3.2. Cumulative incidence and rates of COVID-19 in patients with oxygen-dependent CRF

The cumulative incidence of COVID-19 was highest during the longer pre-alpha and delta/omicron periods (Fig. 2, Table 2). In both oxygen-dependent CRF and the general population, the cumulative incidence of critical COVID-19 infections was highest during the pre-alpha period and the cumulative incidence of any COVID-19 infection as well as the proportions of mild disease were highest during the delta/omicron periods (Fig. 2, Table 2). During the shorter alpha period, the cumulative incidence of new infection was lowest but the incidence rate of infections was highest (Fig. 2, Table 2).

In comparison with the general adult population, severe/critical disease was much more common among patients with oxygen-dependent CRF during all periods (all $p < 0.0001$). The occurrence of any new COVID infection was more similar to the background population, but slightly more common among patients with oxygen-dependent CRF during the pre-alpha period ($p = 0.002$), and less common in the alpha and delta/omicron periods (p for both <0.0001).

3.3. Risk factors for COVID-19 and for severe or critical disease in oxygen-dependent CRF

Higher age, cardiovascular disease and renal disease were identified as risk factors for contracting any COVID-19 infection and for developing a severe/critical disease, and in addition, hypertension was a risk factor for severe/critical disease. During the pre-alpha period, age above 80 years and cardiovascular disease were statistically significantly associated with COVID-19 infection, and age above 80 with the progression to severe/critical COVID-19. During the alpha period, cardiovascular disease was significantly associated with being infected as well as developing a severe/critical disease. During the delta/omicron periods, renal disease was significantly associated with having COVID-19 as well as developing a severe/critical COVID-19. Patients with age 76–80 years and with hypertension were found to be significantly associated with developing severe or critical disease during the delta/omicron variant period (Table 3).

3.4. Impact of COVID-19 on mortality in oxygen-dependent chronic respiratory failure

After the end of the pre-alpha period and after the end of the alpha period, the one-year mortality risk after laboratory-confirmed COVID-19 among patients with oxygen-dependent CRF was significantly higher than among patients with oxygen-dependent CRF and no COVID-19 infection (HR 1.79; [95% CI] 1.27 to 2.53 and 1.43; 1.03–1.99), respectively (Table 4). In addition, male sex, higher age and cardiovascular disease were independent risk factors for mortality in both periods. Renal disease was a risk factor for mortality only in the pre-alpha period (Table 4).

4. Discussion

The primary findings of this study are: A) The cumulative incidence of laboratory-confirmed COVID-19 infection in patients with oxygen-dependent CRF was higher than in the general population only during the first nine months of the pandemic (the pre-alpha period). B) If infected by SARS-COV-2, severe/critical disease was almost ten times higher in patients with oxygen-dependent CRF than in the general population during the entire pandemic. C) Among patients with oxygen-

Table 1
Baseline characteristics for Swedish patients with oxygen-dependent CRF, by pandemic period and laboratory-confirmed COVID-19 or not during the period.

	Pre-alpha period		Alpha period		Delta/omicron period	
	Jan 1-Dec 31, 2020 (N at risk = 1771)		Jan 1-Mar 31, 2021 (N at risk = 1649)		Apr 1, 2021–May 31, 2022 (N at risk = 1610)	
Patient characteristics (n (%))	No COVID-19 during period (n = 1657)	COVID-19 during period (n = 114)	No COVID-19 during period (n = 1601)	COVID-19 during period (n = 48)	No COVID-19 during period (n = 1484)	COVID-19 during period (n = 126)
Male sex	602 (36.3%)	34 (29.8%)	585 (36.5%)	18 (37.5%)	535 (36.1%)	47 (37.3%)
Age						
18–70	344 (20.8%)	20 (17.5%)	369 (23.0%)	8 (16.7%)	346 (23.3%)	36 (28.6%)
71–75	368 (22.2%)	14 (12.3%)	373 (23.3%)	13 (27.1%)	352 (23.7%)	26 (20.6%)
76–80	445 (26.9%)	23 (20.2%)	447 (27.9%)	11 (22.9%)	426 (28.7%)	29 (23.0%)
≤81	500 (30.1%)	57 (50.0%)	412 (25.7%)	16 (33.3%)	360 (28.4%)	35 (27.8%)
Level of education*						
Primary	706 (43.3%)	63 (56.3%)	668 (42.3%)	20 (43.5%)	624 (42.7%)	50 (40.7%)
Secondary	707 (43.4%)	37 (33.0%)	686 (43.4%)	21 (45.7%)	635 (43.4%)	53 (43.1%)
Tertiary	217 (13.3%)	12 (10.7%)	225 (14.2%)	5 (10.9%)	203 (13.9%)	20 (16.3%)
Main cause of CRF**						
Airway disease	1155 (69.8%)	91 (79.8%)	1141 (71.5%)	32 (66.7%)	1052 (71.1%)	88 (70.4%)
Parenchymal disease	214 (12.9%)	8 (7.0%)	210 (13.2%)	8 (16.7%)	195 (13.2%)	15 (12.0%)
Cardiovascular disease	173 (10.5%)	11 (9.6%)	143 (9.0%)	5 (10.4%)	141 (9.5%)	9 (7.2%)
Other	112 (6.8%)	4 (3.5%)	102 (6.4%)	3 (6.3%)	91 (6.2%)	13 (10.4%)
Comorbidity						
Respiratory disease	1565 (94.4%)	109 (95.6%)	1383 (86.4%)	46 (95.8%)	1261 (85.0%)	116 (92.1%)
Hypertension	1002 (60.5%)	76 (66.7%)	900 (56.2%)	29 (60.4%)	806 (54.3%)	82 (65.1%)
Cardiovascular disease	755 (45.6%)	65 (57%)	566 (35.4%)	30 (62.5%)	499 (33.6%)	58 (46.0%)
Obesity	143 (8.6%)	9 (7.9%)	135 (8.4%)	7 (14.6%)	120 (8.1%)	19 (15.1%)
Diabetes	73 (4.4%)	7 (6.1%)	56 (3.5%)	4 (8.3%)	51 (3.4%)	7 (5.6%)
Renal disease	48 (2.9%)	4 (3.5%)	37 (2.3%)	2 (4.2%)	21 (1.4%)	10 (7.9%)

Diabetes denotes diabetes type 2 with complications. Abbreviations: COVID-19 = corona virus disease 2019, CRF = chronic respiratory failure, LTOT = long-term oxygen therapy. *Missing data for level of education: n = 29, 24 and 25 in respective period. **Missing data for underlying main cause of CRF: n = 3, 5 and 6 in respective period.

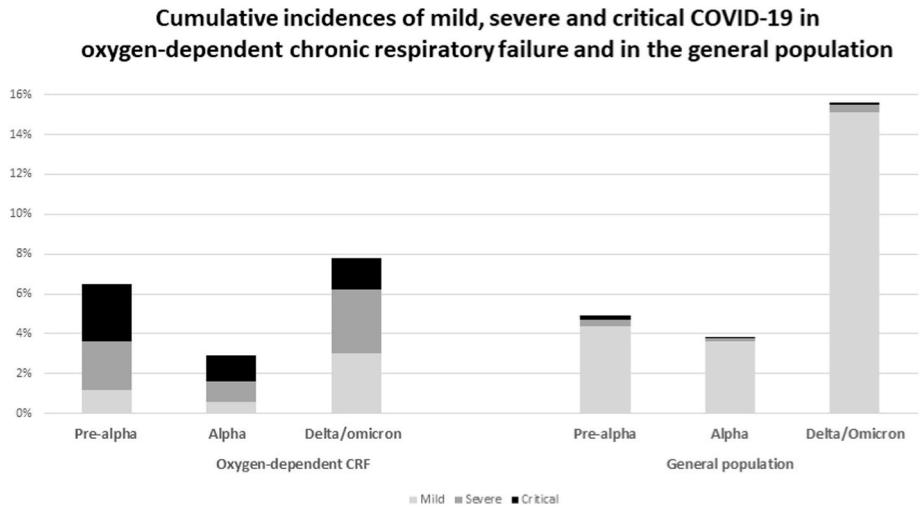

Fig. 2. Distribution of cumulative incidence of mild (no hospitalisation), severe (hospitalised at common ward), and critical (admitted to intensive care unit (ICU) or fatal within one month of laboratory confirmation) in oxygen-dependent CRF and general population, during different periods of the pandemic. *Abbreviations: COVID-19 = corona virus disease 2019, CRF = chronic respiratory failure.*

dependent CRF; age, cardiovascular disease and renal disease were identified as risk factors for laboratory-confirmed COVID-19, and COVID-19 infection was associated with increased one-year mortality risk.

The finding that severe/critical COVID-19 was more common in patients with respiratory failure than in the general population is not surprising, as chronic respiratory disease is a well-known risk factor for both hospitalisation and mortality in COVID-19 [18]. The fact that even the overall ocurrence of any COVID-19 infection in CRF was slightly elevated in the pre-alpha period may be in line with the general observation that the Swedish health care system was not able to protect the elderly and frail as well as intended from infection during this first period [19]. Access to protective equipement like masks and new working routines in elderly care together with the start of the vaccination program reduced the infection rate in this population subgroup significantly [19].

The subsequent lower incidence of any COVID-19 infection in patients with CRF compared with the population during the alpha and delta/omicron variant periods could also be explained by a strict behavior with isolation and avoiding contagious contact among patients with CRF during these phases of the pandemic, out of fear for the consequences noted during the pre-alpha period. The increasing number of

Table 2
Cumulative incidence and rates of any and severe/critical laboratory-confirmed COVID-19 infection during the three periods studied, for patients with oxygen-dependent CRF and in the general adult population.

	Any COVID-19 infection		Severe/critical COVID-19 infection	
	Oxygen-dependent CRF	General population	Oxygen-dependent CRF	General population
Pre-alpha period				
Cumulative incidence (cases/people at risk)	6.4%	4.9%	5.1%	0.5%
Rate (cases/1000 person-years)	64.2	48.6	51.2	4.5
Alpha period				
Cumulative incidence (cases/people at risk)	2.9%	3.8%	2.3%	0.2%
Rate (cases/1000 person-years)	118.1	152.1	93.5	8.1
Delta/omicron period				
Cumulative incidence (cases/people at risk)	7.8%	15.5%	4.8%	0.5%
Rate (cases/1000 person-years)	67.1	133.1	41.0	3.9

Numbers at risk in oxygen-dependent CRF: Pre-alpha period n = 1771, alpha period = 1649, delta/omicron period n = 1610. Numbers at risk in the general population: Pre-alpha period n = 8 457,722, alpha period = 7 958,923, delta/omicron period n = 7 640,518. *Abbreviations: COVID-19 = corona virus disease 2019, CRF = chronic respiratory failure.*

mild infections both in patients with CRF and in the general population during the delta/omicron period should be explained by increased immunity by mass-vaccination and previous infection, changed recommendations for SARS-CoV 2 PCR-samplings in the general population, and early antiviral treatments. However, as the Swedish population had free access to COVID-test for both symptomatic and asymptomatic testing during most of the investigated time periods, we do not believe that changes in testing policy should have influenced the comparative analyses of COVID-19 incidences in patients with LTOT and the general population.

Our findings that higher age, cardiovascular disease and chronic renal disease were the major risk factors for COVID-19 are in agreement with previous studies reporting age and several comorbid conditions including respiratory disease to be associated with severity of disease in COVID-19 in the general population [18]. That comorbid chronic

Table 4
Association of laboratory-confirmed COVID-19 infection with one-year mortality in oxygen-dependent CRF.

Patient characteristics	One-year mortality after pre-alpha period	One-year mortality after alpha-variant period
	Deceased during Jan 01, 2021 to Dec 31, 2021: n = 501	Deceased during Apr 01, 2021 to March 31, 2022: n = 533
	Patients at risk; n = 1731	Patients at risk: n = 1703
	HR (95%CI)	HR (95%CI)
Laboratory-confirmed COVID-19	1.79 (1.27–2.53)	1.43 (1.03–1.99)
Male sex	1.31 (1.10–1.57)	1.28 (1.08–1.53)
Age groups		
18–70	Ref	Ref
71–75	1.34 (0.99–1.81)	1.36 (1.03–1.79)
76–80	1.48 (1.11–1.97)	1.27 (0.97–1.67)
≥81	2.26 (1.72–2.99)	2.20 (1.69–2.86)
Education		
Primary	1.06 (0.81–1.40)	1.25 (0.95–1.66)
Secondary	1.09 (0.82–1.43)	1.27 (0.96–1.69)
Tertiary	Ref	Ref
Comorbidity		
Respiratory disease	0.85 (0.66–1.10)	0.89 (0.70–1.13)
Hypertension	1.23 (1.01–1.49)	1.13 (0.94–1.36)
Cardiovascular disease	1.26 (1.04–1.52)	1.31 (1.09–1.57)
Obesity	0.76 (0.54–1.08)	0.78 (0.56–1.09)
Diabetes	1.10 (0.72–1.67)	1.15 (0.76–1.74)
Renal disease	2.35 (1.53–3.61)	1.66 (1.00–2.77)

Diabetes denotes diabetes type 2 with complications. Abbreviations: CI = confidence interval, COVID-19 = corona virus disease 2019, CRF = chronic respiratory failure, HR = hazard ratio.

Table 3
Risk factors for any and severe/critical laboratory-confirmed COVID-19 infection in patients with oxygen-dependent CRF during different studied periods of the pandemic.

Patient characteristics	Any COVID-19			Severe/critical COVID-19		
	Pre-alpha	Alpha	Delta/omicron	Pre-alpha	Alpha	Delta/omicron
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Male sex	0.85 (0.57–1.28)	1.19 (0.65–2.17)	1.13 (0.78–1.65)	0.97 (0.62–1.50)	1.48 (0.76–2.88)	1.17 (0.73–1.88)
Age groups						
18–70	Ref	Ref	Ref	Ref	Ref	Ref
71–75	0.66 (0.33–1.31)	1.93 (0.75–4.95)	0.83 (0.49–1.41)	0.81 (0.36–1.81)	1.65 (0.60–4.55)	0.94 (0.52–1.72)
76–80	0.85 (0.46–1.57)	1.33 (0.50–3.53)	0.69 (0.41–1.16)	1.18 (0.56–2.41)	1.13 (0.39–3.24)	0.36 (0.17–0.74)
≥81	1.95 (1.14–3.32)	2.00 (0.77–5.14)	1.31 (0.79–2.16)	2.54 (1.34–4.81)	1.37 (0.48–3.92)	1.00 (0.53–1.86)
Education						
Primary	1.49 (0.80–2.77)	1.21 (0.45–3.23)	0.89 (0.53–1.50)	1.80 (0.85–3.81)	2.11 (0.48–9.31)	1.07 (0.54–2.15)
Secondary	1.05 (0.55–2.02)	1.38 (0.52–3.66)	0.92 (0.55–1.55)	1.39 (0.64–3.04)	3.10 (0.72–13.3)	1.13 (0.57–2.25)
Tertiary	Ref	Ref	Ref	Ref	Ref	Ref
Comorbidity						
Respiratory disease	1.38 (0.56–3.40)	2.85 (0.69–11.9)	1.76 (0.91–3.38)	1.42 (0.52–3.81)	4.51 (0.61–33.2)	1.60 (0.73–3.52)
Hypertension	1.14 (0.76–1.72)	0.86 (0.46–1.62)	1.47 (0.99–2.19)	1.17 (0.74–1.85)	0.88 (0.44–1.78)	2.14 (1.26–3.62)
Cardiovascular disease	1.54 (1.04–2.27)	2.98 (1.57–5.63)	1.39 (0.95–2.03)	1.62 (1.05–2.51)	3.10 (1.52–6.32)	1.21 (0.75–1.96)
Obesity	0.82 (0.40–1.66)	1.57 (0.67–3.69)	1.39 (0.82–2.37)	0.93 (0.44–1.97)	0.48 (0.11–2.05)	1.51 (0.80–2.85)
Diabetes	1.25 (0.52–2.97)	1.54 (0.53–4.48)	1.25 (0.56–2.76)	1.38 (0.57–3.32)	1.72 (0.51–5.85)	1.37 (0.53–3.51)
Renal disease	1.10 (0.39–3.10)	1.68 (0.40–7.15)	4.72 (2.39–9.32)	1.32 (0.46–3.75)	1.24 (0.17–9.37)	4.82 (2.12–11.0)

Diabetes denotes diabetes type 2 with complications. Abbreviations: CI = confidence interval, COVID-19 = corona virus disease 2019, CRF = chronic respiratory failure, HR = hazard ratio. *Missing data for level of education: n = 29, 24 and 25 in respective period. **Missing data for underlying main cause of CRF: n = 3, 5 and 6 in respective period.

respiratory disease per se was not significantly associated with higher risk could be explained by the fact that almost all patients in our study population had respiratory disease, giving severely reduced statistical power. Only a minority of patients had chronic respiratory insufficiency based mainly on underlying cardiovascular disease and no comorbid lung disease.

The finding of increased one-year mortality risk after a COVID-19 infection in patients with oxygen-dependent CRF, is consistent with other studies reporting excess mortality in patients with COVID-19 both in the general population as well as in susceptible disease groups such as patients with cancer and mental disorders [20–22]. The risk was moderately increased, which may be due to the fact that mortality overall is very high in patients with oxygen-dependent CRF. We found no studies from other countries exploring the mortality risk after COVID-19 in patients with pre-existing CRF. Assessment of the mortality risk after COVID-19 in the general population is complex, but the reported excess mortality risk in Sweden was higher than in many other countries during the first wave [23–25] and more consistent with other European countries seen over the entire pandemic period [26–28].

Finally, our findings that male sex, higher age, cardiovascular disease and renal disease were independently associated with mortality in patients with LTOT, are consistent with other studies of both respiratory failure and of all patients with COVID-19 [10,29].

4.1. Strengths and limitations

Major strengths of our study are that the data include all laboratory-confirmed COVID-19 cases across Sweden with prospective follow-up using mandatory national outcome register data and that the Swedevox registry provides national data with high validity against records on about 85% of all people with ongoing LTOT before and during the pandemic, increasing the generalisability of our findings.

Limitations of our study include lack of complete population-based data on other potential confounders such as smoking, but using education level as a covariate may at least partly have compensated for this. In addition, we did not address the effects of preexisting immunity induced by vaccination or an undiagnosed previous COVID-19 infection. Finally, the study period is limited to the last of May 2022. However, during the spring of 2022 the laboratory testing of COVID-19 decreased in Sweden, and we believe further data on COVID-19 infection would be less reliable for the analyses presented here as they would reflect the true incidence of COVID-19 less well.

5. Implications and need of future research

The most important clinical knowledge from this study is that for patients with oxygen-dependent CRF, treated with LTOT, health strategies at least at later stages of the pandemic managed to keep the incidence of COVID-19 infection similar to or below the general population incidence, although critical disease continued to be more common due to their underlying frailty. In spite of increased mortality risk after COVID-19, the proportion of patients with mild disease is increasing even in this group.

The somewhat inconsistent results that the risk of COVID-19 in CRF was higher than in the general population during the first phase but lower during the following periods, implicates that precautions to avoid being infected are still important in areas where virus transmission is ongoing. However, the results of this study demonstrate a lower intrinsic risk for progression to critical disease over time, and may thus allow physical training and social contacts to a higher extent in vaccinated patients. This could be important for health-related quality of life and other patient-related outcomes among patients with LTOT.

6. Conclusion

In patients with oxygen-dependent CRF, the proportion diagnosed with moderate/COVID-19 was higher compared with the general population during all variant of concern periods, and COVID-19 is associated with excess one-year mortality in this patient group. The cumulative incidence of COVID-19 was highest during the delta/omicron period but the proportion of mild disease increased during the study period and was highest in the delta/omicron period.

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CRediT authorship contribution statement

Josefin Sundh: Conceptualization, Formal analysis, Methodology, Writing – original draft. **Andreas Palm:** Conceptualization, Methodology, Writing – review & editing. **Mirjam Ljunggren:** Conceptualization, Methodology, Writing – review & editing. **Össur Ingi Emilsson:** Conceptualization, Methodology, Writing – review & editing. **Ludger Grote:** Conceptualization, Methodology, Writing – review & editing. **Sara Cajander:** Conceptualization, Methodology, Writing – review & editing. **Huiqi Li:** Conceptualization, Methodology, Writing – review & editing. **Fredrik Nyberg:** Conceptualization, Methodology, Writing – review & editing. **Magnus Ekström:** Conceptualization, Methodology, Writing – review & editing.

Declaration of competing interest

There is no conflict of interest.

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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.2023.107392.

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