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Incidence and severity of SARS-CoV-2 infection in lung transplant recipients in the Omicron era

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may cause serious illness in lung transplant recipients. We aimed to investigate incidence and severity of SARS-CoV-2 infection in lung transplant recipients in the Omicron era. We conducted a retrospective study investigating COVID-19 incidence and outcomes among lung transplant recipients between December 27, 2021, and October 31, 2022, in Denmark. We performed COX regression analysis of potential risk factors with hospitalization as an endpoint. Among 236 included patients, 108 had a first positive SARS-CoV-2 polymerase chain reaction during a total of 133 person-years of follow-up, resulting in an incidence rate of 813 per 1000 person-years (95% confidence intervals (CI) 670–977). The cumulative incidence of hospitalization was 24.1% (95% CI 26-32.1) and admission to the intensive care unit was 3.7% (95% CI 0.1–6.3). The 30-day mortality of recipients with a SARS-CoV-2 infection was 0.9% (95% CI 0–2.7). We found that the incidence rate of patients with SARS-CoV-2 infection was markedly higher, whereas the mortality rate was lower in the omicron era compared to earlier reports for lung transplant recipients conducted in the delta era. On the other hand, a substantial proportion of patients were hospitalized, suggesting a continuous impact on this patient population.
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The coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused severe illness world-wide and is responsible for numerous deaths.[1] While the virus is largely contagious even before onset of symptoms, it usually causes mild upper respiratory infection affecting sinuses

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and the throat in younger individuals and in the healthy population.[2,3]

In solid organ transplant (SOT) recipients, COVID-19 has had severe consequences compared to the general population, likely due to the immunosuppressive treatment[4] and probably to some extent due to the higher burden of comorbidities in this patient population.[5,6] In the early period of the pandemic, COVID-19 led to fatal outcomes in 1 out of 5 SOT recipients.[7] In comparison, the risk of COVID-19 related hospitalization and death among SOT recipients was approximately 50% and 80% lower in the Omicron era compared to previous variants.[4,8] Despite these improvements, COVID-19 remained one of the major causes of premature death due to a preventable and treatable disease in SOT recipients.[9]

Lung transplant recipients may be particularly vulnerable as the graft is the main target organ of SARS-CoV-2 and the infection can potentially lead to prolonged lung allograft dysfunction.[10–12] A previous study from 2020 reported that 84% of the lung transplant recipients with COVID-19 required some degree of respiratory support and one-third were transferred to the intensive care unit.[11,13] In late 2020 and 2021 when vaccinations became available, all COVID-19 outcomes improved in the lung transplanted population.[14] Fewer patients experienced respiratory failure, there were fewer intensive care unit (ICU) admissions and need for ventilator support and fewer deaths. However, mortality was still relatively high among vaccinated lung transplant recipients with 6% having a fatal outcome.

The initial wave of infections caused by the Omicron variant has been reported to be more contagious, but to cause less severe outcomes in the general population compared to prior strains.[4,15] This development may be due to multiple factors such as the implementation of vaccination programs, increasing natural immunity, and decreasing virulency of emerging variants. However, whether these observed differences are identical in lung transplant recipients remain unclear. Studies evaluating the effect of Omicron in lung transplant recipients are scarce. In a national study including all adult lung transplant recipients in Denmark, we aimed to investigate the incidence and severity of SARS-CoV-2 infection in the Omicron era.

Materials and methods

Patients and study design

We performed a retrospective cohort study investigating adult lung transplant recipients, who were transplanted at the University Hospital of Copenhagen, Rigshospitalet between June 18, 1992, and December 1, 2021. The patients were followed from December 27, 2021, to a first positive SARS-CoV-2 PCR, death or October 31, 2022, whichever came first.

The vast majority of the recipients were vaccinated with the BNT162b1 Pfizer-BioNTec; 2 recipients received another vaccine and were excluded.

Rigshospitalet is the national lung transplant center responsible for all lung transplantations performed in Denmark and thus, the present study is a national study including all lung transplantations performed in Denmark in the study period.

In Denmark, the management of patients with COVID-19 followed the consensus guidelines published by the Danish Society of Infectious Diseases. These guidelines recommend criteria for outpatient treatment, treatment during admission, and isolation regimes during hospital visits or hospitalization. In brief, patients belonging to a high-risk population, for example, lung transplant recipients who had a positive SARS-CoV-2 polymerase chain reaction (PCR) in a throat swab, were invited to the outpatient clinic and recommended pre-emptive treatment with a 3-day course of remdesivir and 1 course of monoclonal antibodies. Recipients with respiratory symptoms or other signs of moderate or severe COVID-19 were admitted to hospital for treatment with supplemental oxygen therapy, dexamethasone, and remdesivir. All recipients were isolated during hospital stay. At admission, a chest X-ray and blood samples including hemoglobin, leukocytes and differential count, thrombocytes, creatinine, electrolytes, albumin, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, international normalized range, coagulation factor II, VII, X, D-dimer, C-reactive protein, and ferritin were measured.

See Figure 1 for flow diagram of included patients.

Endpoints and definitions

Baseline date was defined as December 27, 2021, and was defined as the beginning of the Omicron era in Denmark. This corresponded to the period where SARS-CoV-2 was no longer considered a critical disease and most COVID-19 restrictions were canceled on February 1, 2022.

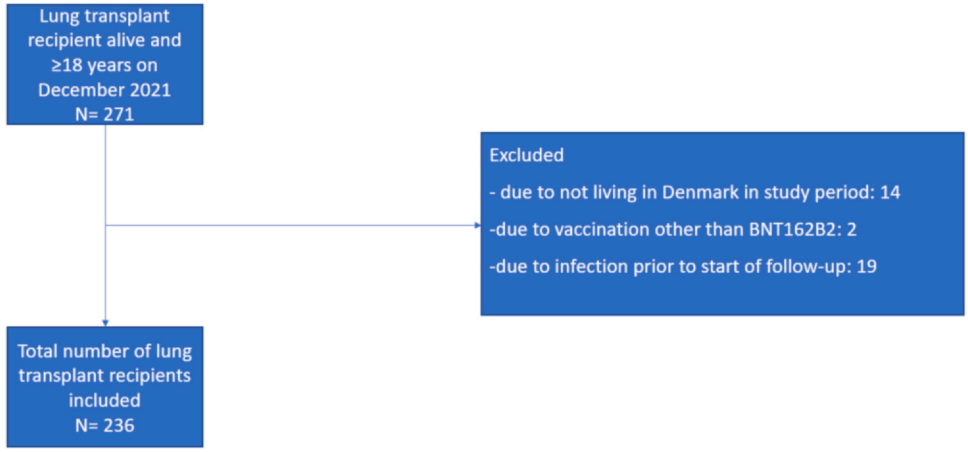

Figure 1 Flow diagram of lung transplant recipients considered for inclusion in the study.

SARS-CoV-2 infection was defined as a positive PCR assay from an oropharyngeal swab during follow-up.

A SARS-CoV-2 reinfection was defined as a positive PCR ≥90 days after a previous positive test.

Patients received either no vaccine doses, 1, 2, 3, 4, or 5 vaccine doses and were considered vaccinated with the specific dose 14 days after a vaccine dose.

Hospitalization was defined as admission to hospital for at least 24 hours with COVID-19 related symptoms within 30 days after a positive SARS-CoV-2 PCR or treatment of COVID-19 related symptoms in an already admitted patient with a positive SARS-CoV-2 PCR.

Admission to ICU was defined as admission to ICU with COVID-19 related symptoms within 30 days after a first positive SARS-CoV-2 PCR.

Outpatient treatment was defined as treatment with 1 course of neutralizing monoclonal antibodies or a 3-day course of remdesivir given to a patient with a positive SARS-CoV-2 PCR, in an outpatient setting.

Data sources

We collected information on demographics, comorbidities, and use of immunosuppression from medical record review. Comorbidities included cardiovascular disease (i.e., hypertension, chronic heart disease, arrhythmia, ischemic heart disease), diabetes mellitus, end-stage renal disease, and a history of cancer.

Use of immunosuppression at baseline and at time of the first positive SARS-CoV-2 PCR among infected patients was collected.

For SARS-CoV-2 infected patients, additional information was collected and included as follows: outpatient treatment with neutralizing antibodies or remdesivir, hospitalization, admission to ICU, and inpatient treatment with oxygen therapy, mechanical ventilation, remdesivir, dexamethasone, and neutralizing antibodies.

SARS-CoV-2 PCR results were collected from MiBa, the Danish National Microbiology Database. MiBa includes all SARS-CoV-2 PCR tests performed at a hospital, at a national test center, or at a general practitioner. Home rapid antigen tests were not collected in MiBa, but the general recommendation was to have the positive rapid antigen test verified with a subsequent PCR test before initiating outpatient or inpatient treatment.

Vaccination status was collected from the Danish Vaccination register, which is a mandatory vaccine registry in Denmark since 2015.

The target level for cyclosporine and tacrolimus is included in Supplementary Table 1.

Statistics

The period between December 27, 2021, and October 2022 was the period of interest for our study. We reported frequencies and proportions of demographics, comorbidities, vaccination status, and positive SARS-CoV-2 PCR tests.

Incidence rates were calculated for patients with a first positive SARS-CoV-2 PCR per 1000 person-years. Byar's approximation was used to calculate 95% confidence intervals (CI).

Cumulative incidence curves for a first positive SARS-CoV-2 PCR during follow-up were performed using the Aalen-Johansen estimator with death as competing risk. Further, cumulative incidence for hospitalization or admission to ICU was calculated among infected patients overall and stratified by vaccination status. Gray's test was used to test for differences in hospitalization and ICU admission between those with less than 4 vaccines vs 4 or more vaccines. The 30-day mortality was calculated using the Kaplan Meier estimator and the log-rank test was used to test for difference between those in the medical care unit vs in intensive care unit.

We performed adjusted COX regression analyses to estimate the hazard ratio (HR) and 95% CI for hospitalization during follow-up. The basic model was unadjusted and included age, sex, number of vaccine doses prior to infection, outpatient neutralizing monoclonal antibody treatment (time-updated), and comorbidities. The adjusted COX regression model included age and number of vaccine doses prior to infection. Score residuals were used to test for the proportional hazard assumption. In the main analyses, recipients with a SARS-CoV-2 infection prior to baseline were excluded. In sensitivity analyses, all recipients were included irrespective of a prior SARS-CoV-2 infection.

Analyses were performed using the R version 4.03 (R Core Team, 2020, Vienna, Austria) and the packages epiR,[16] survival,[17] prodlim,[18] fmsb,[19] timereg,[20] and cmprsk.[21]

Approvals

The study was conducted following the Declaration of Helsinki, and according to Danish legislation, the retrieval of data without collection of informed consent was approved by the institutional review board at the Center for Regional Development (R-20051155).

Results

Study population and baseline characteristics

From December 2021 to October 2022, 236 lung transplant recipients were alive and included. The median time from lung transplantation to start of follow-up was 6.2 years (interquartile range (IQR) 3.4–11.0). Table 1 shows the demographics and comorbidities for all patients. Median age was 58 years (IQR 50–64) and 50% were males. The vaccination status for the entire population at last follow-up was unvaccinated in 2.1%, less than 4 vaccine doses received in 13.1%, and 4 or more vaccine doses in 84.8%. There was no difference in the proportion of number of vaccines among those infected and those not infected at time of last follow-up.

Table 1 Clinical Characteristics of Lung Transplant Recipients at Baseline

Characteristics	Total (n =236)
Age at baseline (median, IQR)	58 [49.8, 64.0]
Sex (male)	118 (50.0)
Time from first transplantation to baseline (median, IQR)	6.2 [3.4, 11.0]
Retransplantation (N, %)	8 (3.4)
Comorbidities (N, %)	
Chronic vascular disease	166 (70.3)
Diabetes mellitus	53 (22.5)
Previous cancer	26 (11.0)
End-stage renal disease	14 (5.9)
Dead during follow-up (N, %)	14 (5.9)

Abbreviations: IQR, interquartile range.

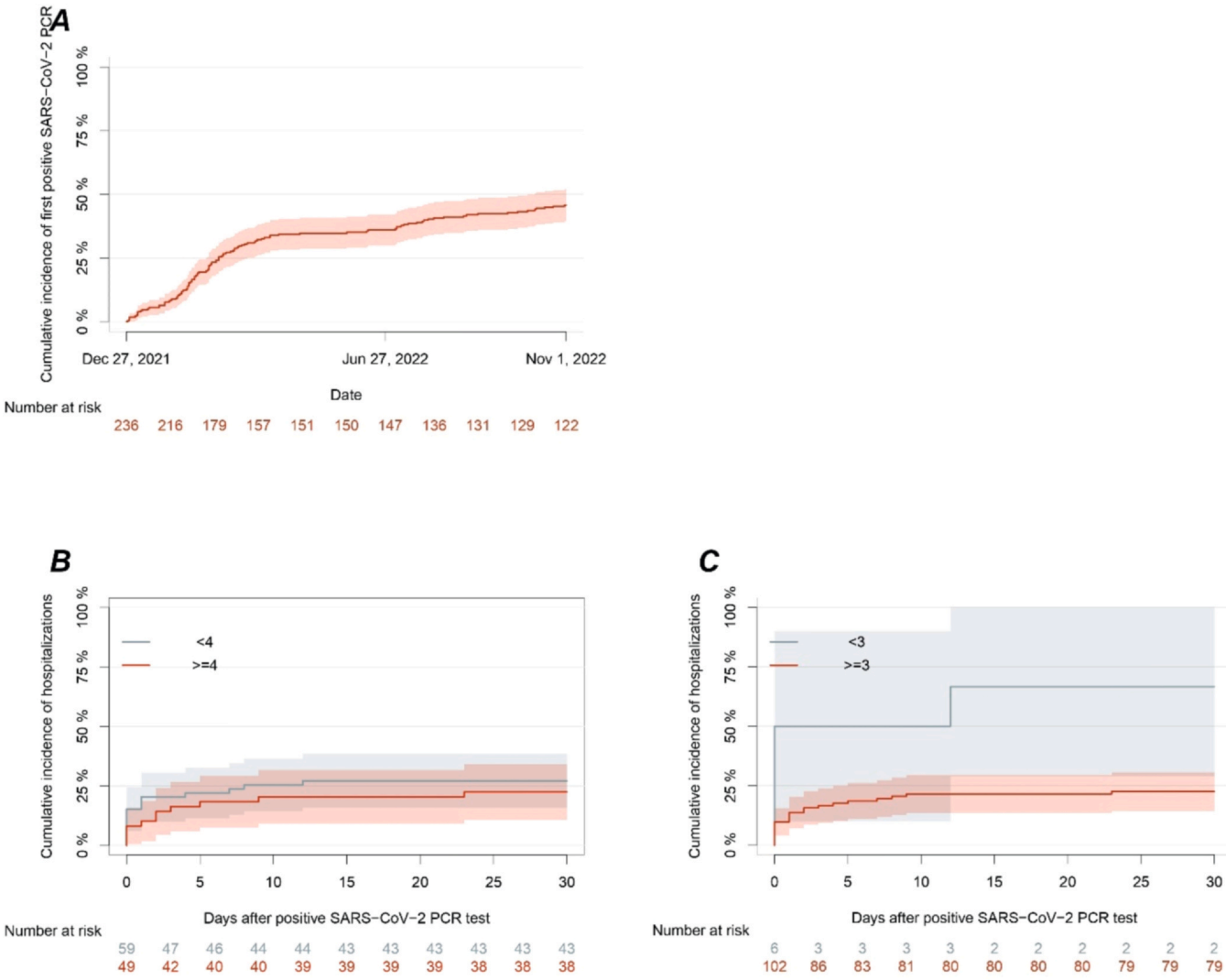

Figure 2 (**A**) Cumulative incidence of first positive SARS-CoV-2 PCR with death as competing risk; (**B**) cumulative incidence of hospitalizations among lung transplant recipients with less than 4 or 4 or more vaccine doses at time of infection 30 days after first positive SARS-CoV-2 infection; (**C**) cumulative incidence of hospitalizations among lung transplant recipients with less than 3 or 3 or more vaccine doses at time of infection 30 days after first positive SARS-CoV-2 infection.

Incidence rate and cumulative incidence of SARS-CoV-2 infection in lung transplant recipients

There was a total of 108 patients with a first positive SARS-CoV-2 PCR during a total of 133 person-years of follow-up, resulting in an incidence rate of 813 per 1000 person-years (95% CI 670–977). Figures 2A shows the cumulative incidence of a first positive SARS-CoV-2 PCR at the end of follow-up and was estimated to 45.8% (95% CI 39.4–52.1). The median time from most recent vaccination to first positive test was 129 days (IQR 55–155). There were additional 4 recipients who had a SARS-CoV-2 reinfection, i.e., an infection prior to baseline and again after baseline during follow-up. These were excluded from the main analyses.

Clinical characteristics of lung transplant recipients at time of first SARS-CoV-2 infection

Table 2 shows the characteristics of lung transplant recipients with a first SARS-CoV-2 infection at the time of infection, stratified by admission to hospital or not. The median number of years from transplantation to first SARS-CoV-2 infection was 7 [3.8, 11.0]. A total of 49 recipients were vaccinated with ≥4 doses at time of first infection. The most common comorbidity was chronic vascular disease (63%), followed by diabetes mellitus (19.4%), and a prior cancer diagnosis (12%). Fifty percent of the recipients had chronic allograft dysfunction (CLAD) at time of first infection. Immunosuppression treatment mainly consisted of prednisolone (100%), calcineurin inhibitors (CNI) (100%), and antimetabolites (74.1%). There was no difference in terms of the assessed characteristics among recipients requiring admission to hospital vs not, Table 2.

Outcomes after first SARS-CoV-2 infection in lung transplant recipients

Among lung transplant recipients with a first SARS-CoV-2 infection 52 (48%) were treated as outpatients only, 27

Table 2 Clinical Characteristics of Lung Transplant Recipients With SARS-CoV-2 Infection, at Time of First Positive PCR Test According to Recipients not Hospitalized and Hospitalized

Characteristics		Hospitalization not required ($n = 81$)	Hospitalized ($n = 27$)	Total ($n = 108$)	p-value
Age at time of infection, median [IQR]		59 [52,65]	61 [56.5, 63.5]	60 [53,65]	0.60
Male sex (%)		42 (51.9)	12 (44.4)	54 (50.0)	0.66
Years from transplantation to infection, median [IQR]		7 [4, 12]	5 [3,8]	7 [3.8, 11.0]	0.08
Immunosuppressant at time of infection (N, %)					
CNI	Tacrolimus	35 (43.2)	11 (40.7)	46 (42.6)	1.00
	Ciclosporin	46 (56.8)	16 (59.3)	62 (57.4)	
mTOR		8 (9.9)	7 (25.9)	15 (13.9)	0.08
Antimetabolite	Azathioprine	12 (14.8)	6 (22.2)	18 (16.7)	0.65
	Mycophenolate mofetile	48 (59.3)	14 (51.9)	62 (57.4)	
	None	21 (25.9)	7 (25.9)	28 (25.9)	
Corticosteroids		81 (100.0)	59 (100.0)	108 (100.0)	NA
Comorbidities at time of infection (N, %)					
Chronic vascular disease		54 (66.7)	14 (51.9)	68 (63.0)	0.25
Diabetes mellitus		16 (19.8)	5 (18.5)	21 (19.4)	1.00
Previous cancer		9 (11.1)	4 (14.8)	13 (12.0)	1.00
End-stage renal disease		4 (4.9)	3 (11.1)	7 (6.5)	0.50
CLAD		40 (49.4)	14 (51.9)	54 (50.0)	1.00
Number of vaccine doses at time of infection					
(N, %)	5	2 (2.5)	1 (3.7)	3 (2.8)	0.10
	4	36 (44.4)	10 (37.0)	46 (42.6)	
	3	41 (50.6)	12 (44.4)	53 (49.1)	
	2	2 (2.5)	2 (7.4)	4 (3.7)	
	1	0 (0.0)	0 (0.0)	0 (0.0)	
	0	0 (0.0)	2 (7.4)	2 (1.9)	

Abbreviations: CLAD, chronic lung allograft dysfunction; CNI, calcineurin inhibitor; IQR, interquartile range; mTOR, mammalian target of rapamycin; PCR, polymerase chanin reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

(25%) were hospitalized, whereas 29 (27%) did not receive treatment for SARS-CoV-2 infection. The median time from a positive test to admission to hospital was 1 day (IQR 0–3.5). Three of 27 recipients who were hospitalized for a first SARS-CoV-2 infection had received outpatient treatment prior to the admission. The most common outpatient treatments were Sotrovimab (42.6%) and Remdesivir (6.5%). Of the 27 hospitalized patients, 21 received a combination of different therapy including remdesivir, dexamethasone, monoclonal antibodies, and supplemental oxygen therapy; 13 received a combination of 2 treatments and 8 received 3 or more treatments, Table 3. The cumulative incidence of hospitalization was 24.1% (95% CI 26–32.1) and admission to the ICU was 3.7% (95% CI 0.1–6.3). All recipients admitted to the ICU were treated with invasive mechanical ventilation. The proportion of lung transplant recipients with severe COVID-19 tended to be higher among recipients with fewer doses of vaccine; the cumulative incidence of hospitalizations among recipients with less than 4 doses of vaccines was 27.1% (95% CI 15.8–38.5) compared to 22.4% (95% CI 10.8–34.9) among recipients receiving ≥4 doses, Figure 2B. Further, the cumulative incidence of hospitalization among recipients with less than 3 doses of vaccines was 76.7 (95% CI 28.9–100) compared to 22.5 (95% CI 14.4–30.7) among recipients receiving ≥3 doses, Figure 2C. The 30-day mortality of recipients with a SARS-CoV-2 infection was 0.9% (95% CI 0–2.7). A total of 14 recipients died during the entire follow-up period, 7 and 7 recipients died during a follow-up time of 65 person-years and 133 person-years in recipients with and without COVID-19, respectively. Among the 14 deceased recipients, 6 died from progression of chronic graft rejection, 5 due to progressing respiratory insufficiency after severe COVID-19 or pneumonia, and 3 from other causes.

Risk factors for hospital admission after first SARS-CoV-2 infection

After adjustment, recipients with 3 (adjusted hazard ratio 0.2 (95% CI: 0.1–0.5)) and with ≥4 doses (adjusted hazard ratio 0.1 (95% CI: 0.0–0.4)) of vaccines had a lower risk of

Table 3 Treatment and Outcomes of Lung Transplant Recipients Hospitalized With COVID-19 at Time of First Positive PCR Test According To Admission to a Medical Care Unit or an Intensive Care Unit

Characteristics		Medical care unit ($n = 23$)	Intensive care unit ($n = 4$)	Total ($n = 27$)	p-value
Years from transplantation to infection, median [IQR]		5 [3,7]	10 [2.8, 18]	5 [3.0, 8.0]	0.63
Immunosuppressant (N, %)					
CNI	Tacrolimus	10 (43.5)	1 (25.0)	11 (40.7)	0.89
	Ciclosporin	13 (56.5)	3 (75.0)	16 (5.3)	
mTOR		5 (21.7)	2 (50.0)	7 (25.9)	0.57
Antimetabolite	Azathioprine	6 (21.7)	0 (0.0)	6 (22.2)	0.11
	Mycophenolate mofetile	10 (43.5)	4 (100.0)	14 (51.9)	
	None	7 (30.4)	0 (0.0)	7 (25.9)	
Corticosteroids		23 (100.0)	4 (100.0)	27 (100.0)	NA
Number of vaccine doses at time of infection (N, %)	5	2 (4.3)	0 (0.0)	2 (3.7)	0.17
	4	7 (30.4)	3 (75.0)	10 (37.0)	
	3	12 (52.2)	0 (0.0)	12 (44.4)	
	2	2 (8.7)	0 (0.0)	2 (7.4)	
	1	0 (0.0)	0 (0.0)	0 (0.0)	
	0	0 (0.0)	1 (25.0)	1 (3.7)	
COVID-19 treatment					
	Supplemental oxygen therapy N (%)	4 (17.4)	(4, 100)	8 (29.6)	< 0.01
	Oxygen therapy, max flow liters/min (median, IQR)	2 (1.8, 2.2)	45 (33.8, 52.5)	9 (2.0, 42.5)	0.02
	Dexamethasone (N, %)	9 (39.1)	3 (75.0)	12 (44.4)	0.43
	Remdesivir (N, %)	19 (82.6)	3 (75.0)	22 (81.5)	1.00
	tixagevimab + cilgavimab (N, %)	2 (8.7)	0 (0.0)	2 (7.4)	1.00
	Sotrovimab (N, %)	12 (52.2)	1 (25.0)	13 (48.1)	0.64
Outcomes					
	Days of hospital stay (median, IQR)	4 (2, 5)	32.5 (5.8, 71.2)	4 (2.5, 6.0)	0.01
	Deceased < 30 days from infection (N, %)	0 (0.0)	1 (25.0)	1 (3.7)	0.31
	Deceased < 60 days from infection (N, %)	0 (0.0)	3 (75.0)	3 (11.1)	< 0.01

Abbreviations: CNI, calcineurin inhibitor; CLAD, chronic lung allograft dysfunction; IQR, interquartile range; max, maximum; mTOR, mammalian target of rapamycin; PCR, polymerase chanin reaction.

hospital admission compared to those with ≤2 doses of vaccines. None of the remaining variables assessed had an impact on hospital admission, Table 4.

In sensitivity analyses including recipients with a prior SARS-CoV-2 infection, results remained consistent with the main results, Supplementary Table 2.

Discussion

In this large cohort study of lung transplant recipients who were infected with SARS-CoV-2 during the Omicron era, we found the incidence rate to be markedly higher, whereas the mortality rate was lower compared to previous reports of earlier strains.[13] We also found that 1 out of 4 lung transplant recipients with COVID-19 required admission to hospital and a substantial proportion of patients were treated in the ICU, suggesting a continuous significant impact on this patient population and the health care system.

Overall, severity and mortality after COVID-19 have improved over the course of the pandemic with better immunity and treatment options.[22] In an early report from 2021 from Sweden, the authors reported ICU admission in 17% of the lung transplant recipients infected and 28-day as well as overall mortality to be 4.2% and 14.8%, respectively.[13] Thus, rates that were at least 4 times higher than rates in the present study. Another early observation from 2022 from the US found high admission and mortality rates among lung transplant recipients (9 of 31 (29%) and 2 of 31 (6.5%), respectively), although the numbers were generally small in this study and should be interpreted with caution.[23] Further, the observations from these 2 studies were from an earlier period of the pandemic where the population immunity may have been lower than in the present study. A recent Swiss study assessed outcome after COVID-19 in lung transplant recipients from March 2020 to July 2022 and reported that one-third of the recipients were hospitalized due to COVID-19 and the 28-day mortality was 2%.[24] Thus, numbers that are more similar to the present study. The authors argue that the transplant recipients at their center were advised to contact their clinicians when tested positive with SARS-CoV-2 and were therefore treated early after onset of symptoms. Another recent study reported a low mortality after Omicron in immunocompromised patients, including lung recipients,

Table 4 Risk Factors for Hospital Admission After First SARS-CoV-2 Infection

	Unadjusted model			Adjusted model		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age at time of infection, per 10 years	1.1	0.8–1.6	0.580	1.3	0.8–2.0	0.37
Male sex	0.8	0.4–1.6	0.455	NA		
Transplanted ≤1 year prior to or after follow-up	1.0	0.2–6.0	0.937	NA		
Number of vaccine doses at time of infection (0 and 1 as reference)						
0 or 1	REF	0.1–2.9	0.429	0.8	0.1–6.7	0.88
2	0.5	0.1–04	< 0.001	0.2	0.1–0.5	0.002
3	0.2	0.1–0.4	< 0.001	0.1	0.0–0.4	< 0.001
≥4	0.1					
Outpatient treatment with monoclonal antibodies	0.4	0.1–1.6	0.130			
Outpatient treatment with remdesivir[a]	NA					
End-stage renal disease	1.9	0.6–6.0	0.252			
Diabetes mellitus	0.8	0.3–2.0	0.757			
Chronic cardiovascular disease	0.6	0.3–1.2	0.123			
CLAD	1.0	0.5–2.2	0.929			

Abbreviations: CI, confidence intervals; CLAD, chronic lung allograft dysfunction; HR, hazard ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]No events in group with remdesivir treatment.

however 20% of the patients were admitted to hospital due to COVID-19.[25] Further, lung recipients compared to other immunocompromised patients were at higher risk of hospitalization after COVID-19 in the cohort. More studies investigating outcome in lung transplant recipients with Omicron is required to further elucidate the evolution of this disease.

In the present study, we observed that the risk of hospitalization due to a SARS-CoV-2 infection was higher in the group with less than 3 vaccine doses compared to those who received 3 or more vaccine doses. These findings could suggest that while the overall incidence of breakthrough infection was high in the present study, there were some indications that repeated vaccinations may have prevented hospitalization in recipients with more vaccine doses. The introduction of vaccines against COVID-19 represents a significant landmark in the pandemic and despite a declining efficacy over time and against new strains, the protection against severe disease seems to remain stable,[26] especially after repeat vaccinations.[27] Immunosuppression has previously been associated with blunted vaccine response and could thus result in lower clinical efficacy in lung transplant recipients. However, reports of the association between number of vaccine doses and severity of COVID-19 have been variable. In a recent study, humoral and T-cell response after vaccination was found to be inferior in SOT patients compared to healthy controls likely due to immunosuppression and further, that treatment with mycophenolate was an independent risk factor for nonresponse to vaccines.[28] Further, a recent study including lung recipients from 8 centers in Germany in the first quarter of 2022 found no association between complete vaccination and severity of COVID-19 which was attributed to a poor vaccine response in this patient group.[29] A study from the US from 2022 including 103 lung recipients with COVID-19 found no association between a minimum of 2 vaccine doses and outcome after COVID-19.[30] On the other hand, Gottlieb et al recently found that vaccine against COVID-19 were associated with lower risk of poor long-term outcome after COVID-19 such as fatigue and multiple symptoms.[31] These studies are all observational studies and thus, causality between vaccination doses and outcome severity cannot be established by these reports. Additional studies are needed to evaluate efficacy of COVID-19 vaccinations among lung transplant recipients in the era of Omicron.

Characterization of SARS-CoV-2 infection in organ transplanted patients was highly demanded in the early period of the pandemic. Experiences from other viral respiratory tract infections raised a concern early in the pandemic that SARS-CoV-2 could severely affect SOT recipients[32,33]. However, others argued that maintenance immunosuppressive medication in organ transplant recipients could perhaps have a protective effect against hyperinflammation in COVID-19 and thus prevent progression to severe disease. Interestingly, previous studies have suggested that older age and underlying comorbidities were associated with mortality and severe outcomes,[6] rather than immunosuppression intensity.[34] As more studies have materialized, more evidence suggest that immunosuppression is a risk factor for severe outcome of COVID-19. Furthermore, there has been reports on long-term adverse effects on lung allograft with a lung function that remained significantly below baseline lung function several months after COVID-19 and showed a restrictive pattern.[12] There has been attempts to prevent progression to severe COVID-19 in lung recipients with pre-exposure prophylaxis with tixagevimab and cilgavimab unfortunately without promising results[35,36]. On the other hand, a 3-day course of early remdesivir has been reported to independently reduce disease severity.[37]

Strengths of our study include the systematic identification of SARS-CoV-2 results and capture of relevant clinical information and vaccination status in a national health care system that include both tertiary care hospitals

as well as community hospitals and test centers. Thus, we were able to calculate incidence and true proportion of patients experiencing severe outcomes.

Despite these strengths, our study has certain limitations. An increasing proportion of infections is now diagnosed at home using rapid antigen tests, making it increasingly difficult to capture mild infections for the purpose of epidemiological studies. However, lung transplant recipients are considered at high risk of severe infection and have been recommended to be treated pre-emptively with remdesivir or neutralizing antibodies and thus were likely to contact their clinicians in the context of SARS-CoV-2 infection to receive guidance regarding their management and immunosuppression treatment. The incidence of SARS-CoV-2 infection is thus a conservative estimate and may in addition underestimate the effect of vaccinations. Further, the present study was performed in a setting with a universal and state-provided health care and thus, these findings may not apply to countries where health care coverage is lower. Adherence to restrictions may vary between recipients. Thus, it is possible that recipients with fewer vaccine doses are more likely to isolate themselves and thus avoid infection which could lead to an underestimation of the incidence of infection in this group. Unfortunately, we did not have access to SARS-CoV-2 serology data or to Omicron sublineage data. The addition of this information could shed light on the underlying mechanism for the incidence and severity of SARS-CoV-2 infection. Unfortunately, we did not have access to pulmonary function tests such as forced expiratory volume in a second or development of cellular rejection data and can thus not evaluate more long-term adverse outcomes after a SARS-CoV-2 infection.

In conclusion, the incidence of SARS-CoV-2 infection is high after lung transplantation, especially after cancellation of COVID-19 restrictions in Denmark. Accordingly, there is a high proportion of lung transplant recipients who need hospitalization or treatment, reflecting a continuous high impact in this patient population and on our health care system.

CRediT authorship contribution statement

Conceptualization, S.D.P., M.P., N.E.W., and S.R.H.; methodology, S.D.P., M.P., S.R.H., N.E.W., D.L.M.; data collection, S.R.H., N.E.W., R.H.L., L.B.L.K., A.R.P.; formal analysis, S.R.H.; investigation, all authors; resources, all authors; data curation, all authors.; writing—original draft preparation, N.E.W.; writing—review and editing, all authors; visualization, S.R.H.; supervision, S.D.P. and M.P.; project administration, N.E.W., S.R.H., S.D.P., M.P.; funding acquisition, S.D.P. All authors have read and agreed to the published version of the manuscript.

Disclosure statement

The 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. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2023.100004.

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