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Original Article

Outcomes of SARS-CoV-2 infection post-solid organ transplantation in the cystic fibrosis population

Julie Semenchuk [a], Yumi Naito [b], Susan C. Charman [b], Siobhán B Carr [c], Jamie Duckers [d], Stephanie Y. Cheng [e], Bruce C. Marshall [f], Albert Faro [f], Alexander Elbert [f], Christopher H. Goss [g], Pierre-Régis Burgel [h], Carla Colombo [i], Marco Salvatore [j], Nataliya Kashirskaya [k], Laura Kirwan [l], Peter G Middleton [m], Lutz Naehrlich [n], Maria Dolores Pastor-Vivero [o], Andreas Jung [p], Egil Bakkeheim [q], Anna Zolin [r], Annalisa Orenti [r], Domenique D. Zomer-van Ommen [s], Marco Zampoli [t], Anne L. Stephenson [a,*], On behalf of the Global CF Registry Collaboration

[a] *Department of Respirology, St. Michael's Hospital, Toronto, Ontario, Canada*
[b] *Cystic Fibrosis Trust, London, United Kingdom*
[c] *Royal Brompton and Harefield Hospitals, part of Guy's and St Thomas's NHS Foundation Trust and Imperial College, London, United Kingdom*
[d] *Cardiff and Vale University Health Board, Cardiff, UK*
[e] *Cystic Fibrosis Canada, Toronto, Canada*
[f] *Cystic Fibrosis Foundation, Bethesda, MD, USA*
[g] *Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Washington Medical Center, Seattle, WA, United States*
[h] *National Reference CF center and Respiratory Medicine, Cochin Hospital APHP and Université Paris Cité, Institut Cochin (InsermU1016), Paris, France*
[i] *Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*
[j] *National Center Rare Diseases, Undiagnosed Rare Diseases Interdepartmental Unit, Italian CF Registry, Istituto Superiore di Sanità, Rome, Italy*
[k] *Research Centre for Medical Genetics, Moscow Regional Research and Clinical Institute ("MONIKI"), Moscow, Russia*
[l] *Cystic Fibrosis Registry of Ireland, Woodview House, University College Dublin, Ireland*
[m] *Bronchiectasis and CF service, Department of Respiratory & Sleep Medicine, Westmead Hospital, Sydney, Australia*
[n] *Department of Pediatrics, Justus-Liebig-University Giessen, Giessen, Germany*
[o] *Cystic Fibrosis Unit, Cruces University Hospital, Biobizkaia Health Institute, Bizkaia, Spain*
[p] *Department of Pulmonology and Cystic Fibrosis Center, Children`s Hospital of Eastern Switzerland, St. Gallen, Switzerland*
[q] *National Resource Centre for Cystic Fibrosis, Department of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway*
[r] *Department of Clinical Sciences and Community Health, Dipartimento di Eccellenza 2023-2027, Laboratory of Medical Statistics, Biometry and Epidemiology "G.A. Maccaccaro", University of Milan, Milan, Italy*
[s] *Dutch CF Foundation (NCFS), Baarn, the Netherlands*
[t] *Department of Paediatrics and Child Health, University of Cape Town, Red Cross War Memorial Children's Hospital, Cape Town, South Africa*

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ABSTRACT

Background: Cystic fibrosis (CF) transplant recipients infected with SARS-CoV-2 are at high risk for hospitalization or death. We aimed to (1) assess whether time since solid organ transplantation impacts severity of SARS-CoV-2 infection and (2) to evaluate the impact of SARS-CoV-2 infection on the slope of lung function trajectory.
Methods: This is a retrospective international cohort study of individuals with CF post-solid organ transplant with a confirmed SARS-CoV-2 infection between January 2020 and December 2021. The primary outcome was death or hospitalization. The secondary outcome was change in lung function trajectory following infection. To assess the impact of time from transplant on the primary outcome, logistic regression was performed while lung function trajectory was assessed using a linear mixed-effects model.
Results: A total of 526 SARS-CoV-2 infections from 19 countries were recorded. The median age at time of infection was 36 years (IQR 29–44). Median time since transplant was 5.8 years (IQR 3.3–10.8). The timing of transplant relative to infection was not significantly associated with hospitalization or death (OR 0.975 CI 0.928–1.025). A higher baseline ppFEV$_1$ was associated with a decreased odds of death or hospitalization (OR

* Correspondence author at. St. Michael's Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8, Canada.
E-mail address: Anne.Stephenson@unityhealth.to (A.L. Stephenson).

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0.989, 95% CI 0.983, 0.995). In a subgroup of participants, lung function trajectory did not change significantly in the year following SARS-CoV-2 infection.

Conclusions: In a diverse global post-transplant CF population, the timing of transplantation was not significantly associated with severe outcomes following SARS-CoV-2 infection. Those with more severe lung disease were at increased risk for worse outcomes and should be monitored closely.

Non standard abbreviations

BMI	Body Mass Index
CF	Cystic Fibrosis
CFRD	Cystic Fibrosis-Related Diabetes
CFTRm	CF Transmembrane Conductance Regulator Modulators
CLAD	Chronic Lung Allograft Dysfunction
COVID-19	Coronavirus Disease 2019
ECMO	Extracorporeal Membrane Oxygenation
GLI	Global Lung Function Initiative
HIC	High-Income Countries
ICU	Intensive Care Unit
IV	Intravenous
LMIC	Low- and Middle-Income Countries
OR / AOR	Odds Ratio / Adjusted Odds Ratio
ppFEV1	Percent Predicted Forced Expiratory Volume in 1 S
pwCF	People with Cystic Fibrosis
REDCap	Research Electronic Data Capture
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

Introduction

In March of 2020, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection was declared a pandemic by the World Health Organization.[1] It was soon identified that both underlying respiratory disease and states of immunosuppression, including solid organ transplantation, were associated with COVID-19 related deaths.[2] Despite people with cystic fibrosis (CF) having underlying lung disease, studies have shown that the majority of individuals with CF who contracted SARS-CoV-2 infection recovered and mortality rates were relatively low.[3–5] Furthermore, a recent study showed there was no clinically meaningful change in lung function or body mass index (BMI) trajectory up to one year following infection in a global non-transplant CF cohort.[6] Despite these reassuring outcomes, certain factors including previous solid organ transplantation increased the risk of hospitalization, new or additional oxygen use and death following SARS-CoV-2 infection in multiple cohorts.[5,7–9]

Initial reports on outcomes following SARS-CoV-2 infection, in solid organ transplant recipients specifically, were descriptive and presented as case series.[10,11] A French study describing outcomes of SARS-CoV-2 infection in the lung transplant population, revealed high rates of hospitalization, critical care admissions and mechanical ventilation early post-transplant, but did not compare this with infections that occurred later in the transplant period.[12] In contrast, a more recent lung transplant cohort in Australia, where most individuals were vaccinated at the time of infection and promptly treated with antiviral therapy, demonstrated lower rates of hospitalization and mortality rates under 10 % with stable lung function trajectory.[13] Interestingly, a recent study of lung transplant recipients reported that underlying CF was associated a milder SARS-CoV-2 infection phenotype highlighting variability in outcomes people with CF (pwCF) may experience.[14] Individuals with CF are historically younger than other transplant recipients with fewer comorbidities but experience higher pseudomonas colonization.[15–17] Given these differences, it is plausible their post COVID-19 outcomes may differ from other post transplant patients.

Although there is data to show that infections in general are more frequent in the early post-transplant period aligning with periods of higher immunosuppression,[18] the relationship between severity of SARS-CoV-2 infection and timing of transplant is less clear.[19] The goals of the current study were (1) to understand whether time since solid organ transplantation impacts the severity of SARS-CoV-2 infection in CF and (2) to evaluate the impact of infection on lung function trajectory post lung transplantation in CF.

Methods

Study design

As described in our previous work, beginning in March 2020, a group of individuals from institutions across the world representing national CF registries came together to form the CF Registry Global Collaboration.[6] The goal was to evaluate the impact of SARS-CoV-2 infection on the health of pwCF. Following this, several additional countries, including those without well-established registries, joined the collaboration. Together, a retrospective longitudinal cohort study of all individuals with CF who contracted SARS-CoV-2 was established. This paper focuses on the sub-group of individuals who received a solid organ transplant.

Data collection and definitions

Individuals with CF who received a solid organ transplant (any type) with documented SARS-CoV-2 infection between January 1, 2020 and December 31, 2021 that occurred after their transplant date were eligible for inclusion. For individuals with multiple infections, only the first infection was used.

The CF Registry Global Collaboration standardized SARS-CoV-2 data collection using an Excel case report form and REDCap database. Data submission varied by country. Most countries with well-established and comprehensive CF registries extracted data from their registries as per provided data specification. The European CF Society Patient Registry (ECFSPR) collected the data with Excel forms and extracted them into a project-specific REDCap database. For most countries without well-established registries, data were collected by the CF clinics using the Excel case report form. All data were submitted using a secure file-sharing platform. De-identified/anonymized data were collected according to each individual nation's CF registry ethics approval or national guidelines.

Primary exposure variable

Time since solid organ transplant at time of SARS-CoV-2 infection was calculated using infection date and transplant date. For those with multiple transplants, the first solid organ transplant (any type) date in the study window was used.

Outcome variables

Primary outcome: The primary outcome was defined as hospitalization or death as a composite outcome. For this analysis, anyone with a solid organ transplant was included. Individuals were excluded if there was missing outcome data, missing data for covariates used in adjusted analysis, and those with percent predicted forced expiratory volume in 1 s ($ppFEV_1$) outliers (<0.5th percentile or >99.5th percentile).

Secondary outcome: Lung function trajectory was the secondary outcome. To assess the change in lung function before and after SARS-

CoV-2 infection, the analysis was limited to those individuals who had received a lung transplant (i.e. lung only and lung-liver transplant recipients). Individuals who received an isolated liver transplantation were excluded from the lung function analysis because these individuals would have native CF lungs and represent a different pulmonary disease state compared to lung transplant recipients. Other exclusions included: individuals with less than one post-lung transplant $ppFEV_1$ measurement within 1-year pre- and 1-year post-SARS-CoV-2 infection, $ppFEV_1$ values that were <0.5th percentile or >99.5th percentile (outliers), and individuals who were recorded as being on a CF transmembrane conductance regulator modulators (CFTRm) when the lung function was measured. Countries submitted the $ppFEV_1$ using GLI 2012 reference equations whenever possible.[20] The date of each $ppFEV_1$ measurement was used to calculate the time since infection which was measured as a continuous variable in years.

Additional variables

Demographic variables recorded were transplant type, age at SARS-CoV-2 infection, sex at birth, race, and genotype. Clinical variables obtained at the time of SARS-CoV-2 diagnosis were vaccination status, CF-related diabetes (CFRD) status (yes/no), prior history of *P. aeruginosa* infection (yes/no), systemic hypertension (yes/no) and pancreatic status (pancreatic insufficiency/ sufficiency). Vaccination status at the time of infection was categorized as fully, partially, not vaccinated, or unknown. Fully vaccinated was defined as the person had received all the recommended dosage(s) for a given vaccination course (for example, Jcovden® is one dose; Comirnaty® is a sequence of two) at least 14 days prior to SARS-CoV-2 diagnosis. Partially vaccinated was defined as the person having not received all the suggested dosages of a multi-dose vaccine course or having completed the initial vaccination course <14 days before SARS-CoV-2 infection. Additional variables collected included intensive care unit (ICU) admission, use of extracorporeal membrane oxygenation (ECMO), mechanical ventilation, and non-invasive ventilation. Using World Bank definitions for 2022 fiscal year, countries with a gross national index per capita less than $12,696 were considered to be low-and-middle income countries (LMIC) and others were considered high-income countries (HIC).[21]

Statistical analyses

Demographic, clinical characteristics, and outcome measures were summarized as frequencies and proportions for categorical variables and median with interquartile range (IQR) for continuous variables. To evaluate the primary outcome of the association between time since transplantation (continuous variable in years) and hospitalization/death a logistic regression model was used. Adjusted odds ratios (AOR), 95 % confidence intervals (CI) and two-sided p-values were used to assess association. Pre-infection $ppFEV_1$, age at time of infection, sex, race, genotype, infection year, CFRD, pancreatic status, country income status were adjusted for in the models where possible and were selected *a priori*.[7] The model used cluster-robust standard errors to account for correlation within countries.[22]

Given hospitalization practices across centers may have varied at different points in the study period, we conducted sensitivity analyses with modified composite outcomes of similar disease severity. The composite outcomes were composed of the following: 1) new oxygen use and/or ICU admission and/or death and 2) new oxygen use and/or ICU admission and/or death and/or non-invasive ventilation (NIV) and/or mechanical ventilation were used. To construct this composite outcome only those who had non-missing data in all outcomes were included in the analysis (i.e. complete case analysis). If an individual had any of the outcomes recorded they were deemed to have had the outcome.

The impact of infection on post-lung transplant lung function trajectory was investigated using a linear mixed-effects model. In the linear mixed-effects model, $ppFEV_1$ was the dependent variable, modeled as a function of time since infection, pre/post-infection status, and their interaction. The impact of SARS-CoV-2 infection on the rate of change in $ppFEV_1$ was estimated using an interaction function between the infection period (pre- vs post-SARS-CoV-2 infection) and time since infection. Given substantial heterogeneity in reported spirometry measurements across patients and centers, restricting the analysis to individuals with multiple measurements in both periods would have excluded a large proportion of the cohort and resulted in a non-representative sample. Therefore, individuals with one FEV_1 measurement in each period were still included as they contributed to the pre- and post-intercepts while those with ≥ 2 pre or post FEV_1 measurements contributed additionally to the slopes. In line with previous studies, age at time of infection, sex, country income status were included, where possible, as control variables.[6] Year of infection (2020 vs 2021) was also included as a pragmatic adjustment to capture broad differences in circulating SARS-CoV-2 variants, treatment availability, and vaccine uptake across the study period; finer temporal stratification was not feasible due to international heterogeneity and data availability.

Sensitivity analyses

We conducted sensitivity analyses (Table S2) to assess the robustness of our findings. These were completed (1) treating time from transplant categorically, (2) removing ppFEV1 from the model, (3) excluding liver transplant recipients, and (4) using imputed case analysis to address missing outcomes. Using our secondary outcome of lung function trajectory, a sensitivity analysis which controlled for additional covariates post-hoc including pancreatic status, genotype, race, CFRD and PI.

Results

Cohort creation

A total of 526 individuals from 19 countries were eligible for inclusion. Demographic and clinical characteristics are presented in Table 1. Of the 526 individuals, SARS-CoV-2 was diagnosed by RT-PCR in 441 (83.8 %), rapid antigen testing in 21 (4.0 %), antibody serology in 34 (6.5 %), radiographically in 2 (0.4 %), and unknown in 25 (5.3 %). The majority of transplants were bilateral lung (n = 478, 90.9 %), with 15 (2.9 %) lung-liver and 33 (6.3 %) liver only. The median time between transplant and infection was 5.8 years (IQR 3.3, 10.8) with 5.7 % acquiring SARS-CoV-2 infection within one year of the transplant.

Four countries did not provide sufficient clinical data on transplant recipients to be included in the final analyses, leaving a total of 15 countries from North America, Europe and Australia (**Table S1**). Cohort creation for both the primary and secondary outcomes are presented in Fig. 1. Individuals could contribute to both cohorts. All countries included in analyses were considered HIC, therefore, country income status was not included in the adjusted models.

Primary outcome: death or hospitalization

A total of 319 individuals who received a solid organ transplant (including lung, lung-liver, and liver only) were included in the primary analysis (Table 1, Fig. 1). The composite outcome of death or hospitalization occurred in 155/319 (48.6 %) individuals with 130 (40.8 %) being hospitalized and 25 (7.8 %) deaths.

Time from transplant to SARS-CoV-2 diagnosis was not significantly associated with death or hospitalization (adj OR 0.975 95 % CI 0.928, 1.025) (Fig. 2). As expected, a higher baseline $ppFEV_1$ was associated with a decreased odds of death or hospitalization (OR 0.989, 95 % CI 0.983, 0.995). Results were unchanged in the sensitivity analyses when time from transplant was treated as a categorical variable, when baseline $ppFEV_1$ was excluded from the analysis and when individuals who underwent isolated liver transplant were excluded (**Table S2**). When individuals undergoing isolated liver transplantation were excluded, the

Table 1
Demographic and clinical characteristics at the time of COVID-19 infection.

	Eligible transplant cohort	Primary analysis	Secondary analysis
Outcome of interest	n/a	Death or hospitalization	Lung function trajectory
Sample size N, %	526	319 (60.6)	236 (44.9)
Sex; n (%)			
Female	274 (52.1)	160 (50.2)	119 (50.4)
Male	252 (47.9)	159 (49.8)	117 (49.6)
Age; Median (IQR)	36.0 (29.0–44.0)	35.0 (29.0–44.0)	36.0 (30.0–44.0)
Age; n (%)			
6–17	15 (2.9)	9 (2.8)	4 (1.7)
18–39	315 (59.9)	195 (61.1)	145 (61.4)
≥40	196 (37.3)	115 (36.1)	87 (36.9)
Transplant type			
Lung	478 (90.8)	282 (88.4)	226 (95.8)
Liver	33 (6.3)	25 (7.8)	0 (0.0)
Lung-liver	15 (2.9)	12 (3.8)	10 (4.2)
Time post transplant (years)	5.8 (3.3–10.8)	5.5 (3.1–10.1)	5.1 (3.0–9.2)
Time post transplant			
≤2 years	87 (16.5)	55 (17.2)	48 (20.3)
3–5 years	161 (30.6)	104 (32.6)	77 (32.6)
6–9 years	116 (22.1)	70 (21.9)	53 (22.5)
10+ years	162 (30.8)	90 (28.2)	58 (24.6)
Race/ethnicity; n (%)			
White	482 (91.6)	294 (92.2)	213 (90.3)
Black	10 (1.9)	6 (1.9)	7 (3.0)
Other	34 (6.5)	19 (5.9)	16 (6.7)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Genotype; n (%)			
Homozygous F508del	260 (49.4)	167 (52.4)	112 (47.5)
Heterozygous F508del	195 (37.1)	119 (37.3)	95 (40.3)
Other	57 (10.8)	33 (10.3)	24 (10.2)
Unknown	14 (2.7)	0 (0.0)	5 (2.1)
Baseline $ppFEV_1$; Median (IQR)	79.5 (63.0–93.0)	78.5 (63.2–92.7)	80.9 (68.1–94.4)
Baseline $ppFEV_1$; n (%)			
<40 %	36 (6.8)	21 (6.6)	6 (2.5)
40–70 %	109 (20.7)	89 (27.9)	62 (26.3)
>70 %	284 (54.0)	209 (65.5)	168 (71.2)
Missing	97 (18.4)	0 (0.0)	0 (0.0)
Baseline BMI (kg/m^2); Median (IQR)	21.3 (19.2–23.7)	21.4 (19.3–23.8)	21.6 (19.7–24.0)
CF-related diabetes; n (%)			
Yes	394 (74.9)	230 (72.1)	176 (74.6)
Missing	11 (2.1)	0 (0.0)	1 (0.4)
P. aeruginosa infection[1]; n (%)			
Yes	264 (50.2)	157 (49.2)	105 (44.5)
Missing	30 (5.7)	25 (7.8)	16 (6.8)
Pancreatic insufficiency; n (%)			
Insufficient	430 (81.8)	293 (91.9)	219 (92.8)
Missing	12 (2.3)	0 (0.0)	0 (0.00)
Systemic Hypertension; n (%)			
No	308 (58.6)	188 (58.9)	127 (53.8)
Yes	183 (34.8)	123 (38.6)	101 (42.8)
Missing	35 (6.7)	8 (2.5)	8 (3.4)
CFTR modulators[2]; n (%)			
No	488 (92.8)	297 (93.1)	236 (100.0)
Elexacaftor-tezacaftor-ivacaftor	18 (3.4)	14 (4.4)	0 (0.0)
Other[3]	8 (1.5)	8 (2.5)	0 (0.0)
Unknown	12 (2.3)	0 (0.0)	0 (0.0)
SARS-Cov-2 Vaccination status			
Fully vaccinated	148 (28.1)	76 (23.8)	58 (24.6)
Partially vaccinated	27 (5.1)	19 (6.0)	11 (4.7)
Not vaccinated	219 (41.6)	137 (43.0)	109 (46.2)
Unknown	132 (25.1)	87 (27.3)	58 (24.6)

[1] Chronic or intermittent infection in the 5 years prior to COVID-19 diagnosis.
[2] Using CFTR modulators at the time of COVID-19 diagnosis.
[3] Other modulators included ivacaftor, lumacaftor-ivacaftor and tezacaftor-ivacaftor

Values are n (%) unless otherwise specified. Proportions are calculated from column totals (n/N) Where no 'Missing' row is included, variables are 100 % complete.

Abbreviations; IQR, interquartile range; CFTR, cystic fibrosis transmembrane conductance regulator; $ppFEV_1$, percent predicted forced expiratory volume in 1 s

relationship with pre-infection $ppFEV_1$ and the primary outcome was unchanged (adj OR 0.950, CI 0.918–0.984). No significant association was seen between death or hospitalization and age, sex, race, year of infection, genotype, CFRD or pancreatic status.

Sensitivity analyses using the following composite outcomes including 1) new oxygen use and/or ICU admission and/or death as well as 2) new oxygen use and/or ICU admission and/or death and/or NIV and/or mechanical ventilation produced results that were consistent with the original analysis. (Table S3)

Secondary outcome: lung function trajectory

A total of 236 lung transplant recipients (lung only and lung-liver) were included in the secondary analysis of lung function trajectory (Fig. 1).

The rate of change in lung function before and after SARS-CoV-2 infection can be seen in Fig. 3. After adjusting for age, sex and year of infection (2020 vs 2021) there was no statistically significant change in rate of change of lung function following SARS-CoV-2 diagnosis (Fig. 3). The absolute difference in the rate of change was −2.35 % per year (95 % CI −6.66, 1.96 %). In a sensitivity analysis, additional covariates were added to the model including CFRD, pancreatic insufficiency, genotype and race which did not change the results (difference in slope of −2.49 %, 95 % CI −6.94 %, 1.97 %).

Data on post-infection outcomes including ICU admissions, use of invasive mechanical ventilation, ECMO, or non-invasive ventilation are summarized for all cohorts in Table 2.

Discussion

In this global retrospective cohort study of transplant recipients with CF, we found no significant association between the time from transplantation and the occurrence of severe outcomes following SARS-CoV-2

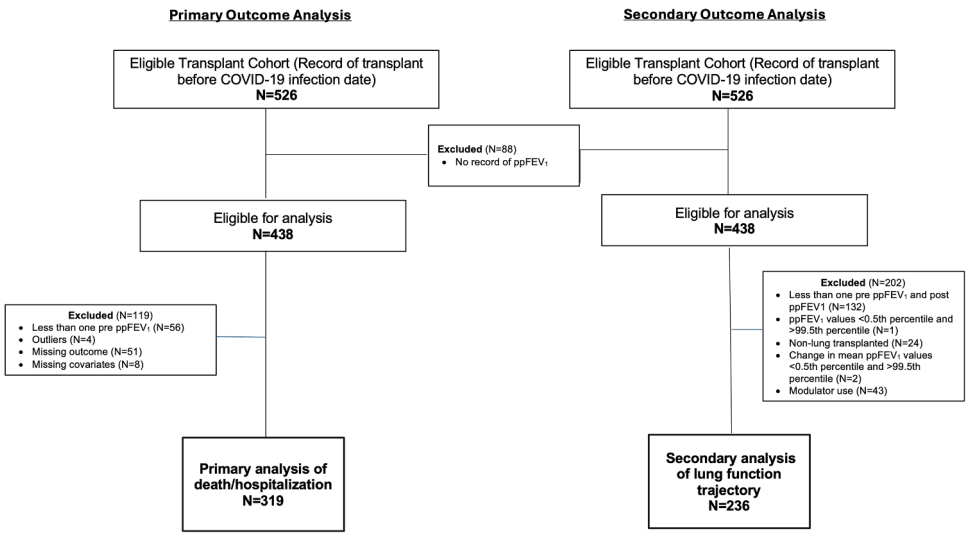

Fig. 1. Study cohort creation.

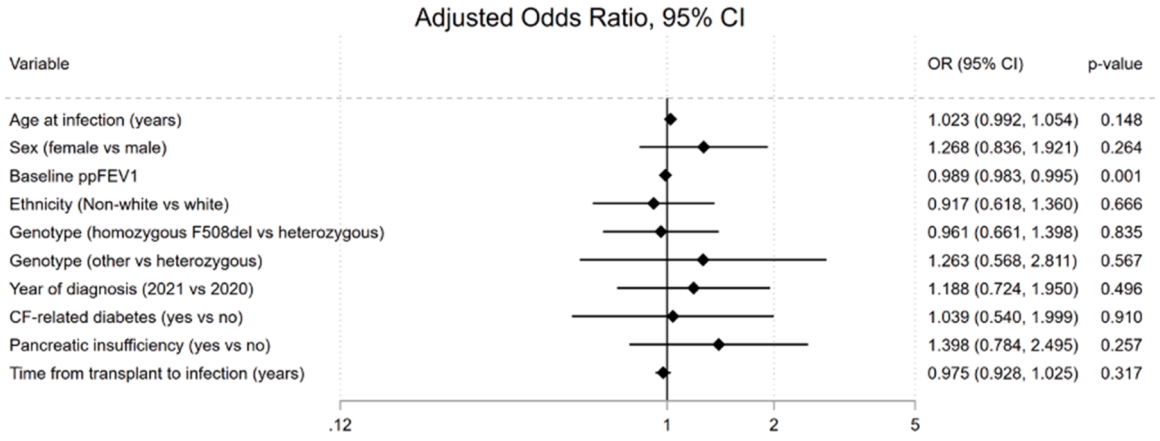

Fig. 2. Risk factors associated with risk of hospitalization or death following COVID-19 infection ($n = 319$).

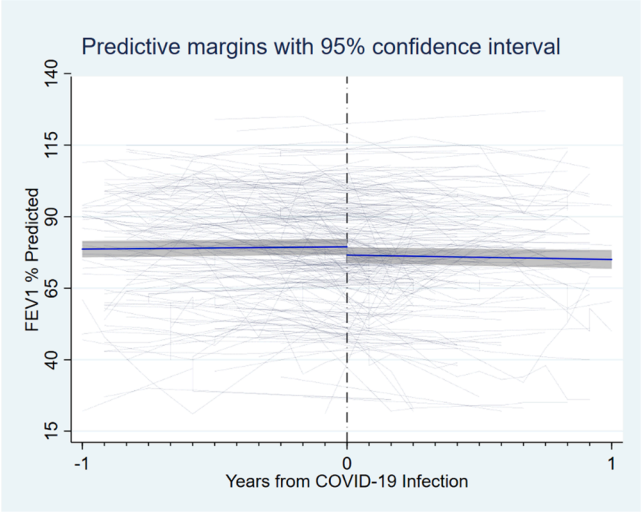

Fig. 3. Rate of change in $ppFEV_1$ pre- and post-COVID-19 infection in lung transplant recipients.

infection. Specifically, developing SARS-CoV-2 sooner after receiving a solid organ transplant did not increase the risk of death or hospitalization. Further there was not enough evidence to say that lung function trajectory changes in the year following SARS-CoV-2 infection in the lung transplant population. Although lung function trajectory becomes negative following COVID-19; neither the pre-infection nor post-infection lung function slopes were significantly different from zero.

In this study, the timing of SARS-CoV-2 infection from transplantation was not a statistically significant risk factor for death or hospitalization regardless of whether this was analyzed as a continuous or categorical variable. Importantly, time since transplantation serves only as an indirect proxy for immunosuppressive burden and does not capture substantial center-level and patient-level heterogeneity in immunosuppression regimens. The spread of time post transplantation was wide in our cohort with approximately 50 % of individuals being transplanted 6 years or more prior to COVID-19 infection and 50 % being transplanted within 5 years in our primary analysis. Our results are similar to a previous large cohort study of 1957 solid organ transplant recipients that failed to find a relationship between time from transplantation and infection severity, though their median time from transplantation was longer at 8.5 years.[19] In a database study done by Kolla et al., the timing of transplantation was inversely associated with

Table 2
Acute outcomes of COVID-19 infection.

	Eligible transplant cohort	Primary analysis	Secondary analysis
Sample size (n)	526	319	236
Death or hospitalization			
Death or hospitalization	229 (43.5)	155 (48.6)	100 (42.4)
None	235 (44.7)	164 (51.4)	104 (44.1)
Missing	62 (11.8)	0 (0.00)	32 (13.6)
Intensive care unit admission			
No	372 (70.7)	256 (80.3)	171 (72.5)
Yes	67 (12.7)	45 (14.1)	24 (10.2)
Unknown	87 (16.5)	18 (5.6)	41 (17.4)
New or additional oxygen[1]			
No	323 (61.4)	217 (68.0)	144 (61.0)
Yes	114 (21.7)	76 (23.8)	52 (22.0)
Unknown	89 (16.9)	26 (8.2)	40 (17.0)
Non-invasive ventilation			
No	419 (79.7)	288 (90.3)	192 (81.4)
Yes	28 (5.3)	15 (4.7)	9 (3.8)
Unknown	79 (15.0)	16 (5.0)	35 (14.8)
Invasive mechanical ventilation			
No	409 (77.8)	278 (87.2)	190 (80.5)
Yes	39 (7.4)	25 (7.8)	11 (4.7)
Unknown	78 (14.8)	16 (5.0)	35 (14.8)
ECMO[2]			
No	433 (82.3)	295 (92.5)	196 (83.1)
Yes	10 (1.9)	6 (1.9)	*
Unknown	83 (15.8)	18 (5.6)	<5

[1] New or additional supplemental oxygen
[2] ECMO=Extracorporeal membrane oxygenation
Proportions are calculated from column totals (n/N).
Additional oxygen, ICU admission, NIV, invasive mechanical ventilation and ECMO are not mutually exclusive and people can appear in more than one group

severe COVID-19 only in those who were transplanted over 10 years prior to their infection date, and no relationship was found with other post-transplant time periods.[23]

Unlike prior studies analyzing timing of transplantation as a risk for more severe infection, most cases in our cohort were lung transplant recipients. Immunosuppression in lung transplantation is generally highest in the early post-transplant period with most centers tapering target levels of calcineurin inhibitors as well as prednisone during the first year.[24–26] There is significant variability in practice however, especially with respect to induction therapy immediately post-transplant.[27] The small number of SARS-CoV-2 infections within the first year post transplant in our study ($n = 30$, 5.7 %) may explain why no relationship with time post-transplantation was detected. Center-to-center variability in immunosuppression protocols may also explain this. Our results are similar to previous findings, that failed to find a relationship between severity of SARS-CoV-2 infection and transplant timing.[28–30]

We demonstrated that a lower pre-infection $ppFEV_1$ was a risk factor for hospitalization or death following COVID-19 in the transplant population. This is similar to data in the non-transplanted CF population[5,7,9], other lung transplant cohorts[28] and those with other chronic lung diseases.[31,32] Further, age, sex, genotype, year of COVID-19 diagnosis, CFRD and pancreatic insufficiency were not associated with higher risk for more severe disease in our study.

Hospitalization and/or death occurred in 60.6 % for our primary cohort and in 44.9 % for our secondary cohort. These hospitalization rates are lower than those reported by Hum et al., who observed 84 % and 66 % hospitalization during two COVID-19 surges between March 2020 and February 2021, prior to vaccine availability.[33] However, it is similar to hospitalization rates during their third surge and when vaccines were available from December 2021 to January 2022 which were 39 %. More recently, Kehara et al. summarized data on lung transplant recipients with SARS-CoV-2 infections from March 2020 to September 2021 which showed hospitalization rates of 67 %, an intubation rate of 25 % and ECMO requirements of 5 %; all significantly higher than our cohort.[34] In this study, the main indications for lung transplantation were pulmonary fibrosis and chronic obstructive pulmonary disease. [34] Therefore pwCF may experience a milder COVID-19 course post-transplant which has been suggested previously.[14]

One of the strengths of this study is the inclusion of transplant recipients of pwCF from 15 countries to describe a global experience. Beyond this, while most studies looking at outcomes of SARS-CoV-2 infection in pwCF have identified transplantation as a risk for more severe disease, this is the first study, to our knowledge, assessing the transplant cohort through comprehensive risk factor and lung function trajectory analyses. Further, by controlling for the underlying native disease in a post-transplant cohort, there is one less confounding factor when interpreting post SARS-CoV-2 outcomes.

We must acknowledge several limitations. Key variables that may have influenced COVID-19 severity and lung function trajectory—such as transplant immunosuppression, chronic lung allograft dysfunction (CLAD), and other respiratory or non-respiratory comorbidities (e.g., obesity, cardiac disease)—were not captured. Time since transplantation is typically used as a pragmatic surrogate for immunosuppression burden; however immunosuppression practices vary substantially across centers and over time,[27] and this unmeasured heterogeneity may have attenuated associations between immunosuppression intensity and COVID-19 severity. As a result, our findings should be interpreted as associations with time since transplant rather than definitive estimates of immunosuppression-related risk, and true relationships between immunosuppressive burden and COVID-19 severity may have been underestimated. Although information on COVID-19-specific therapies and vaccination status were collected, due to a large amount of missing data they were not included in the final analysis. The COVID-19 pandemic influenced transplantation practices across the globe, resulting in a decrease in kidney, lung, liver and heart transplants.[35] As a result, fewer early post-transplant infections may have been captured, potentially masking a signal. Changes in transplant practice could have also influenced candidate selection. We were however able to adjust for many covariates in both our risk factor and lung function trajectory analysis which did not alter results. We could not account for changes in SARS-CoV-2 variants over the study period as we did not have the granularity of data and we acknowledge that our data were captured early-on in the pandemic when there were more severe variants and fewer people vaccinated.[36] In addition, specific protocols for anti-viral treatment for solid organ transplant recipients were recommended in the setting of SARS-CoV-2 infection developed over the study period which could have impacted the hospitalization rates, particularly if people were admitted for IV preventative therapies. Our sample size was relatively small, however for the lung function trajectory analysis we utilized a repeated measures design which maximizes the power to detect a difference. Finally, our study was limited to one year of follow up and therefore the long term effects of COVID-19 on other lung function parameter and CLAD remain unknown.

Through this work, we demonstrated, in a diverse global population, that the timing of transplantation was not significantly associated with hospitalization/death following SARS-CoV-2 infection in the post-transplant CF population. However, lower baseline $ppFEV_1$ was a risk factor for more severe disease which is noteworthy. We did not find sufficient evidence to say there was a significant change in lung function trajectory following SARS-CoV-2 infection. Future studies are needed to determine the impact of infection on long-term transplant-specific outcomes such as CLAD.

Rate of change analyses for $ppFEV_1$ following COVID-19 infection.

Covariates	n	Pre-infection slope (ppFEV$_1$/year)	Post-infection slope (ppFEV$_1$/year)	Slope difference (ppFEV$_1$/year)	Slope difference p value
None	236	0.82 (−1.91, 3.54)	−1.54 (−4.76, 1.69)	−2.35 (−6.66, 1.96)	0.284
Sex and age	236	0.81 (−1.92, 3.53)	−1.51 (−4.74, 1.72)	−2.32 (−6.63, 1.99)	0.291
All specified covariates[1]	236	0.82 (−1.91, 3.54)	−1.54 (−4.77, 1.70)	−2.35 (−6.66, 1.96)	0.285
Additional covariates[2]	231	1.23 (−1.59, 4.05)	−1.26 (−4.57, 2.06)	−2.49 (−6.94, 1.97)	0.274

[1] All pre-specified covariates as outlined in the Methods section were used including age, sex and infection year.
[2] In addition to the specified covariates, the covariates CF related diabetes, pancreatic insufficiency status, genotype and race were added to the analysis
ppFEV$_1$ = percent predicted forced expiratory volume in 1 s

Author contributions

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Data Curation: All authors.
Formal Analysis: SCC, YN.
Funding acquisition: ALS, CHG, AJ, SYC.
Methodology: SCC, YN, SYC, ALS.
Supervision: ALS.
Writing-original draft: JS.
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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2026.02.009.

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