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A multinational report to characterise SARS-CoV-2 infection in people with cystic fibrosis

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ABSTRACT

Information is lacking on the clinical impact of the novel coronavirus, SARS-CoV-2, on people with cystic fibrosis (CF). Our aim was to characterise SARS-CoV-2 infection in people with cystic fibrosis. Methods: Anonymised data submitted by each participating country to their National CF Registry was reported using a standardised template, then collated and summarised. Results: 40 cases have been reported across 8 countries. Of the 40 cases, 31 (78%) were symptomatic for SARS-CoV-2 at presentation, with 24 (60%) having a fever. 70% have recovered, 30% remain unresolved at time of reporting, and no deaths have been submitted. Conclusions: This early report shows good recovery from SARS-CoV-2 in this heterogeneous CF cohort. The disease course does not seem to differ from the general population, but the current numbers are too small to draw firm conclusions and people with CF should continue to strictly follow public health advice to protect themselves from infection.

1. Introduction

A cluster of cases of pneumonia of unknown origin presented in Wuhan, China in early December 2019; the cause was subsequently found to be a novel coronavirus, now named SARS-Cov-2 [1]. This new virus is highly transmissible and has resulted in a pandemic with over 2 million confirmed infections and more than 145,000 deaths in humans in 185 countries [2].

SARS-CoV-2 presents with variable symptoms from a mild cough, fever or flu-like illness that can resolve in a few days to a more serious pneumonia that can lead to adult respiratory dis-

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tress syndrome, respiratory failure, a cytokine storm and multiple organ failure [3]. The outcome appears age dependant with children frequently having minimal or mild symptoms or being asymptomatic whereas elderly people tend to have significant mortality and morbidity. Estimates of the Case Fatality Rate (CFR) after adjustments for demography and under-ascertainment in China were 1.38% (1.23%–1.53%), with substantially higher rates in older age groups: 6.4% (5.7%–7.2%) in those over 60 years old as compared to 0.32% (0.27%–0.38%) in those under 60 years [4]. Comorbidities such as diabetes mellitus, hypertension and chronic lung disease have been reported to be associated with a worse outcome and higher CFR [5]. There is uncertainty regarding the true prevalence of SARS-CoV-2 and therefore the Infection Fatality Rates (IFR).

Cystic fibrosis (CF) is a multisystem genetic condition resulting in progressive chronic lung disease and multiple comorbidities including CF-related diabetes mellitus (CFRD) in up to one third of people [6], liver disease and malnutrition. In 2009–2010 the H1N1 influenza pandemic resulted in significant morbidity in most people with CF who contracted the infection [7]. Many countries have categorised people with CF as highly vulnerable to SARS-CoV-2 and have advised "shielding" or "cocooning" (staying at home at all times and avoiding face-to-face contact with anyone outside the household) to try to minimise the risk of people with CF contracting the virus. The impact of acute infection with SARS-CoV-2 in people with CF is not known [8]. Here we report the clinical characteristics and outcome of 40 people across 8 countries with CF who have tested positive for SARS-CoV-2 infection.

2. Methods

The 'Cystic Fibrosis Registry Global Harmonization Group' set up extra-ordinary meetings at the outset of the SARS-CoV-2 pandemic, meeting twice monthly to share case reports and case capture methods. CF Registries in each participating country contacted all CF care centres to request data be provided. Once consensus was reached on key reporting requirements, a template was circulated to each participating country. Eight countries were able to obtain relevant ethics approvals and submit anonymised data by the cut-off date of 13 April 2020.

Anonymised data were collected, identifying neither the person with cystic fibrosis nor the treatment centre. Cases were identified as people with a definitive diagnosis of cystic fibrosis who tested positive for SARS-CoV-2 between 1 February – 13 April 2020. Cases submitted with CT scans suggestive of SARS-CoV-2 but without a positive test result for the virus were excluded. Unresolved cases were included, reported as such, and countries were asked to report zero cases as appropriate.

The information collected included sex, age, genotype group, body mass index (BMI), most recent 'Best' FEV1% predicted, treatment data, CF related complications, microbiology, transplant, pregnancy and current health status. Data collection is ongoing, and additional countries have committed to ongoing case capture and follow up.

2.1. Information governance

Each participating country was responsible for ensuring Research Ethics Board or institutional approvals were in place for this work. A nominated country representative collated all known cases and added them to a standardised template, accurate at 13 April 2020.

3. Results

A total of 8 countries are participating in the study; Australia, Canada, France, Ireland, Netherlands, New Zealand, UK and US. New Zealand reported zero cases. Table 1 reports the demographics, clinical attributes and symptom presentation of the 40 cases reported broken down into underlying CF severity according to lung function. Of the 40 cases, 31 (78%) were symptomatic for SARS-CoV-2 at presentation, with 24 (60%) having a fever. The median age was 33 years (range 15–59 years), with only one patient aged under 16 years. 38% had CFRD and 70% were reported to have chronic bacterial pulmonary infection, of which 71% included *Pseudomonas aeruginosa* (PsA). One was pregnant and has recovered, delivering a healthy baby. Eleven reports have been from post-lung transplant patients, who are on average 6 years (range: 1–15 years) post their most recent transplant (one patient has more recently

Table 1
Demographics, clinical attributes and symptom presentation.

			Best FEV1% predicted range							
	ALL ($N = 40$)*		<40 ($N = 5$)		40–70 ($N = 12$)		>70 ($N = 11$)		Post Tx** ($N = 11$)	
	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
Age, years	33	15–57	28	20–58	32	20–57	26	15–57	40	27–49
	N	%	N	%	N	%	N	%	N	%
Male	17	43	1	20	5	42	3	27	7	64
Homozygous F508del	17	43	3	60	3	25	4	36	6	55
Aged ≥18 years	38	95	5	100	12	100	10	91	11	100
Aged ≥40 years	13	33	2	40	3	25	2	18	6	55
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Best FEV1% pred***	70	18–114	31	18–38	59	40–70	89	80–106	83	50–114
	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
BMI, kg/m^2	22	16–34	19	18–23	22.5	16–33	23	20–34	21	16–24
	N	%	N	%	N	%	N	%	N	%
BMI >30 kg/m^2	2	5	0	0	1	8	1	9	0	0
Chronic PsA	20	50	5	100	6	50	5	45	4	36
CFRD	15	38	1	20	6	50	6	55	2	18
CFTR modulator†	14	35	3	60	5	42	6	55	0	0
	N	%	N	%	N	%	N	%	N	%
Symptomatic	31	78	3	60	9	75	8	73	10	91
Fever	24	77	3	100	6	67	6	75	8	80
Dyspnoea	10	32	0	0	1	11	5	63	4	40
Altered cough	15	48	2	67	5	56	3	38	5	50

Table 2
Interventions and outcomes.

	No transplant		Post-transplant**		All	
	N = 29	%	*N* = 11	%	*N* = 40	%
Interventions						
Intensive care (SARS-COV-2 related)	1	3	3	27	4	10
New supplemental oxygen	7	24	6	55	13	33
Invasive ventilation	0	0	1	9	1	3
Outcomes						
Clinically recovered	22	76	6	55	28	70
Unresolved at time of report	7	24	5	45	12	30
Died	0	0	0	0	0	0

*One patient, who has not received a lung transplant, is not able to perform spirometry testing, so is excluded from the 'Best FEV1% predicted range' counts. This patient only appears in the 'ALL' counts.
**Lung, Lung and Liver or Lung and Kidney (consecutive) transplants (Tx).
***Best FEV1% predicted. Countries provided the most recent available pre-infection best FEV1% predicted. Measurements are from 2019 or 2020.
ᵗIvacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, or elaxacaftor/tezacaftor/ivacaftor [9].

undergone a kidney transplant). Table 2 describes medical interventions and outcomes. 25 (63%) of people were started on new antibiotics: 10 acute oral antibiotics and 17 IV antibiotic therapy. Two people started on both oral and IV antibiotics.

13 (33%) patients required oxygen and 1/40 patient required invasive ventilatory support. Four (10%) were admitted to an Intensive Care Unit (ICU) for SARS-CoV-2 related reasons (two remain in ICU at time of reporting). 14 people were reported as using CFTR modulators. Of these, 1 (7%) was admitted to ICU and 3 (21%) required oxygen. 28 of the cases have been reported as clinically recovered from SARS-CoV-2, with no deaths reported to a participating Registry.

4. Discussion

These early data suggest that the course of disease in CF may not be as severe as expected from initial data from patients with other underlying lung diseases. This CF population infected with SARS-CoV-2 are heterogeneous, with a wide range of lung function, complications, and chronic respiratory infections. No apparent themes or specific risk factors for the contraction or severity of SARS-COV-2 are detectible at this stage. No fatalities have been reported in this series, despite the presence of low lung function, lung transplantation listing or receipt, pregnancy and serious comorbidities amongst the cohort. The only patient to date needing invasive ventilation associated with SARS-CoV-2 has been in an individual who was post-transplant.

The median age of this cohort at 33 years is higher than the general CF population, for comparison the median age in the UK CF population was 20 in 2018 [6]. This is due to the low number of reported cases in the paediatric population. This adult predominance in CF reflects the picture for SARS-CoV-2 in the general population [8]. 43% of this cohort are male, unlike current reports of 60–75% of admitted patients in the general population being male [10]. The median BMI of adults aged 20 or over in the UK CF population is 22.5 kg/m^2 [6], it was 22 kg/m^2 in this SARS-CoV-2 cohort.

Eleven (28%) people with CF in the cohort have had a lung transplant. Post-transplant patients with CF may be over-represented in this cohort as a result of transplant centre protocols to investigate new respiratory symptoms, a change in lung function and a new temperature in post-transplant patients. This is borne out by the high proportion (91%) of post-transplant patients tested due to presentation of symptoms rather than routine screening.

A high proportion of this SARS-CoV-2 cohort received acute oral or IV antibiotics during their infection. Antibiotics are not known to be effective against SARS-CoV-19 and were administered to treat the underlying chronic respiratory infection or exacerbation.

To date, incidence of SARS-CoV-2 amongst the CF population (0.07%) appears to be lower than the average incidence derived on 13 April from the general populations of participating countries (0.15%) [11]. All countries within this study are at different stages of the pandemic, as such general population rates will differ. The apparent lower rate in CF may be partly attributable to the lower average age of the CF population, or lags in reporting. It may also be due to people with CF adopting "shielding", "protective self-isolation" or "cocooning" (staying at home at all times and avoiding face-to-face contact with anyone outside the household) earlier and being more effective at mitigating the risk of cross infection than the general public. It has also been suggested that the chronic respiratory disease population is 'primed' for reducing risk of exposure due to learned behaviors or standard of care therapies [12].

4.1. Limitations

The SARS-CoV-2 pandemic is a rapidly evolving global situation with participating countries at different phases of the epidemic. Not all countries in Europe were able to participate in this study, notably some countries with substantial experience of SARS-CoV-2. Reasons for non-participation were lack of a national data collection infrastructure, reporting lag, or delays gaining ethics approvals for data sharing. For participating countries, this method of case capture is not exhaustive and may not identify all cases. This may be due to inability to obtain all required data or test results prior to the deadline, or delayed reporting by clinical teams to their respective Registry. Cases where CT scans were highly suggestive of SARS-CoV-2 but the patient had not tested positive for the virus were excluded from this study. In some cases, multiple tests had been performed, but reports of 20–30% false-negative SARS-CoV-2 test rates should be noted [13]. There are varying testing protocols across the participating countries and ascertaining the number of tests conducted in the CF population is hard, meaning the denominator of people with CF who have been exposed to SARS-CoV-2 is not known.

Caution must be exercised when interpreting these early results, and the limitations of this study born in mind. We cannot combine the national case series to estimate mortality because of heterogenous testing policies and reporting processes across different countries.

5. Conclusions

The outcomes of this early cases of SARS-CoV-2 in 40 people with CF, reported across 8 countries, have been better than initially predicted based on previous respiratory pandemics. However, the medium and long-term impact of SARS-CoV-2 amongst infected patients is still not known.

The absence of mortality amongst the population may be linked to the relatively low incidence of SARS-CoV-2 amongst the CF pop-

ulation. This could be attributed to effective shielding techniques, but it is too early to state this with confidence.

Declaration of Competing Interest

The authors have no conflicts of interest to declare relating to this work.

Appendix. Global Registry Harmonization Group

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