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Short communication

The global impact of SARS-CoV-2 in 181 people with cystic fibrosis

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ABSTRACT

With the growing SARS-CoV-2 pandemic, we need to better understand its impact in specific patient groups like those with Cystic Fibrosis (CF). We report on 181 people with CF (32 post-transplant) from 19 countries diagnosed with SARS-CoV-2 prior to 13 June 2020. Infection with SARS-CoV-2 appears to exhibit a similar spectrum of outcomes to that seen in the general population, with 11 people admitted to intensive care (7 post-transplant), and 7 deaths (3 post-transplant). A more severe clinical course may

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be associated with older age, CF-related diabetes, lower lung function in the year prior to infection, and having received an organ transplant. Whilst outcomes in this large cohort are better than initially feared overall, possibly due to a protective effect of the relatively younger age of the CF population compared to other chronic conditions, SARS-CoV-2 is not a benign disease for all people in this patient group.

Many people with cystic fibrosis (CF) have so far avoided infection with SARS-CoV-2. As individuals with CF and their families struggle with decisions such as whether it is safe to return to school, work, or clinic, there is a lack of data to inform them ([1], *Lancet Respiratory Medicine* 2020). We previously described the clinical characteristics and outcome of SARS-CoV-2 infection in 40 adults with CF from 8 countries [2].

Herein, the 'Cystic Fibrosis Registry Global Harmonization Group' reports this update of 181 people with CF from 19 countries reported by their CF team to have a diagnosis of acute SARS-CoV-2 infection. Diagnostic criteria were a positive nasal/throat PCR and/or CT scan, and/or firm clinical diagnosis in a hospital setting. Exclusion criteria for this study were an incidental finding of raised serum SARS-CoV-2 antibodies, because timing of the acute infection would not be known. Cases were recorded up to the 13 of June 2020 (including the 40 cases previously reported). These countries cover a total CF population of over 85,000, and across Europe the proportion of people with CF living with a transplant is 6.1%, ranging across different countries from 0 to 13% [3]. At the time of data collection, participating countries were experiencing the pandemic differently with varying total case numbers (coronavirus.jhu.edu/map.html).

The cases were divided into two subgroups, 149 non-transplanted people with CF, and 32 people post-transplant. P-values from Pearson's chi-square tests are presented in the non-transplant cohort for CF-related variables of interest relevant to SARS-CoV-2 associations observed in the wider non-CF population.

The characteristics of the 149 people in the non-transplant cohort were; median age 24 years (range 0–74 years), 48% male, 36% were homozygous and 37% were heterozygous for F508del, 24% had CF-related diabetes (CFRD), 43% were taking CFTR modulator therapy, and median best FEV_1 prior to infection was 73% predicted, (range 18–123%) (Table 1). 82% were symptomatic of SARS-CoV-2 and 47% were hospitalised.

The post-transplant cohort comprised 28 lung-only transplants, 1 lung and kidney transplant, 1 lung and liver transplant, and 2 liver-only transplants; median age was 38 years (range 9–50 years), 63% were male, 59% were homozygous and 31% heterozygous for

Table 1
Key characteristics of people with CF diagnosed with SARS-CoV-2 before 13th June 2020, by transplant status.

	Overall	**Non- transplant**	**Post-transplant**
	N = 181	*N* = 149	*N* = 32
Sex; n (%[1])			
Female;	90 (50)	78 (52)	12 (38)
Male;	91 (50)	71 (48)	20 (63)
Age; median (range)	27 (0–74)	24 (0–74)	38 (9–50)
Age; n(%[1])			
<18	53 (29)	51 (34)	2 (6)
18–39	92 (51)	75 (50)	17 (53)
≥40	36 (20)	23 (15)	13 (41)
Genotypes; n (%[1])			
Homozygous F508del	72 (40)	53 (36)	19 (59)
Heterozygous F508del	65 (36)	55 (37)	10 (31)
Other	42 (23)	40 (27)	2 (6)
CFRD; n (%[1])			
No	90 (50)	83 (56)	7 (22)
Yes	56 (31)	36 (24)	20 (63)
Missing[2]	35 (19)	30 (20)	5 (16)
Pseudomonas; n (%[1])			
No	80 (44)	68 (46)	12 (38)
Yes	92 (51)	76 (51)	16 (50)
Missing[2]	9 (5)	5 (3)	4 (13)
Best FEV_1; median (range)	76 (18–123)	73 (18–123)	80 (19–114)
Best FEV_1; n (%[1])			
<40	24 (13)	23 (15)	1 (3)
40–70	47 (26)	39 (26)	8 (25)
>70	89 (49)	73 (49)	16 (50)
Missing[2]	21 (12)	14 (9)	7 (22)
BMI; median (range)	21 (13–38)	21 (13–38)	21 (16–29)
Missing[2]*; n (%[1])*	29 (16)	28 (19)	1 (3)

Where no 'Missing' row is included, variables are 100% complete.
[1] Column proportions are calculated (n/N) for each descriptive category from the column total of each cohort.
[2] Proportions of missing data are calculated from the column total of each cohort.

Table 2
Outcomes and characteristics of people with CF diagnosed with SARS-CoV-2 before 13th June 2020, non-transplant patients ($N = 149$).

	Hospitalisation			Supplemental O2			ICU		
	Total non-missing	No	Yes	Total non-missing	No	Yes	Total non-missing	No	Yes
	$N = 141$	$N = 75$	$N = 66$	$N = 101$	$N = 78$	$N = 23$	$N = 110$	$N = 106$	$N = 4$
Female; n (%[1])	76	38 (50)	38 (50)	55	42 (76)	13 (24)	58	56 (97)	2 (3)
Male; n (%[1])	65	37 (57)	28 (43)	46	36 (78)	10 (22)	52	50 (96)	2 (4)
Age; median (range)	24 (0–74)	23 (0–74)	24 (1–57)	24 (0–62)	22 (0–58)	30 (1–62)	23.5 (0–62)	23.5 (0–62)	30 (7–42)
Age; n (%[1])									
<18	48	29 (60)	19 (40)	34	31 (91)	3 (9)	40	39 (98)	1 (3)
18–39	70	36 (51)	34 (49)	48	36 (75)	12 (25)	52	51 (98)	1 (2)
≥40	23	10 (43)	13 (57)	19	11 (58)	8 (42)	18	16 (89)	2 (11)
Genotype; n (%[1])									
Homozygous F508del	52	29 (56)	23 (44)	40	32 (80)	8 (20)	42	39 (93)	3 (7)
Heterozygous F508del	51	24 (47)	27 (53)	38	29 (76)	9 (24)	41	40 (98)	1 (2)
Other	37	21 (57)	16 (43)	22	16 (73)	6 (27)	26	26 (100)	0 (0)
CFRD[2]; n (%[1])									
No	81	42 (52)	39 (48)	79	59 (75)	20 (25)	82	79 (96)	3 (4)
Yes	36	16 (44)	20 (56)	22	19 (86)	3 (14)	22	21 (95)	1 (5)
Pseudomonas[2]; n (%[1])									
No	63	40 (63)	23 (37)	49	40 (82)	9 (18)	54	54 (100)	0 (0)
Yes	73	31 (42)	42 (58)	52	38 (73)	14 (27)	56	52 (93)	4 (7)
Best FEV_1; median (range)	73 (18–122)	83.5 (27–122)	57 (18–115)	71.5 (18–122)	79.5 (18–122)	57 (26–94)	72 (18–123)	73 (18–123)	63.5 (55–79)
Best FEV_1[2]; n (%[1])									
<40	22	7 (32)	15 (68)	14	8 (57)	6 (43)	14	14 (100)	0 (0)
40–70	38	11 (29)	27 (71)	30	19 (63)	11 (37)	31	28 (90)	3 (10)
>70	69	50 (72)	19 (28)	48	43 (90)	5 (10)	52	51 (98)	1 (2)
BMI; median (range)	21 (13–38)	21 (13–38)	21 (13–34)	21 (13–38)	21 (13–38)	19.5 (15–29)	20.5 (13–38)	20.5 (13–38)	21.5 (15–26)

[1] *Row proportions are calculated from the total non-missing in each outcome.*
[2] *Where the values in a descriptive category do not add up to the overall column total (CFRD, Pseudomonas, Best* FEV_1*) this indicates incomplete data in the given descriptive.*

F508del, 63% had CFRD, median best FEV_1 prior to infection was 80% predicted (range 19–114%) (Table 1). 93% were symptomatic and 74% were hospitalised.

When comparing the post-transplant to non-transplant patients, a significantly higher proportion of people with an organ transplant were hospitalised compared with non-transplants (20 (74%) vs 66 (46%), $p = 0.009$). Similarly, 7 (25%) post-transplant patients were admitted to ICU vs. 4 (4%) non-transplant patients, 12 (52%) required supplemental oxygen vs. 23 (23%), and 4 (17%) required NIV vs. 3 (3%).

Age is known to be an important determinant of outcome following SARS-CoV-2 infection in the general population, with an increase in mortality after age 50 years [4]. Although the proportion being hospitalised appeared to increase with age in the non-transplant CF cohort (37% under 18 years were admitted, 47% aged 18–39, and 57% aged over 40 years) this was not statistically significant ($p = 0.374$) (Table 2).

Male sex has been shown to be associated with more severe SARS-CoV-2 infection in the general population [5,6]. In the non-transplant CF cohort, male sex did not appear to increase the chance of being hospitalised, with 50% of females and 43% of males needing admission ($p = 0.412$). In post-transplant patients there were twice as many males in the cohort, with 83% having been hospitalised compared with 56% of females (Table 3).

Diabetes is also known to be a risk factor for more severe infection in the general population ([7]., *Lancet Diabetes Endocrinol* 2020). In the non-transplant cohort, a higher proportion of people with CFRD were hospitalised (56%) compared with people without CFRD (48%) ($p = 0.460$) (Table 2). In people with CFRD vs without CFRD, 14% vs 25% required additional oxygen, 5% vs 4% were admitted to ICU, and 1 (5%) vs 2 (3%) required non-invasive ventilation (NIV). In the post-transplant cohort, the proportion of people admitted to hospital was similar in people with CFRD and people with no CFRD (79% vs 71%) (Table 3).

In the non-transplant cohort, of those with best FEV_1 prior to illness less than 40% predicted, 68% were hospitalised, compared with 71% hospitalised with FEV_1 40–70%, and 28% when FEV_1 >70%. This shows higher proportions of people with best FEV_1 <70% predicted were hospitalised ($p<0.001$) (Table 2).

Seven deaths were recorded in the entire cohort, 5 male and 2 female. One of the seven deaths, in a non-transplant patient, was reported by the clinical team as being related to advanced cystic fibrosis, not SARS-CoV-2. In the non-transplant cohort, 4 deaths were recorded, 2 of which had a best FEV1 the year prior to infection of <40% predicted and 2 with 40–70% predicted. In this cohort, one death was in a patient aged <18, one was aged 18–39 and 2 were aged 40 years or over. 3 of the 4 non-transplant deaths were in people with CFRD.

In the post-transplant cohort, 3 deaths were recorded. In this cohort, one of the deaths was recorded in a person aged 18–39 and 2 were in people aged 40 years or over. One death was in a patient with CFRD, one with no CFRD and one with CFRD status unknown.

Univariate tests of association should be interpreted with caution as they do not allow for potential confounding from other covariates and are based on varying completeness of descriptive and outcome variables. Due to low numbers, univariate tests were not completed for the post-transplant cohort. Another limitation is that we have not captured data on people with CF who have been infected with SARS-CoV-2 but not presented to their CF teams, or with only a positive serological test (with no clinical symptoms reported earlier). CF Registries around the globe are beginning to capture data on blood antibody testing, and it will be important to examine how these data compare to the general population. The long-term health impact of SARS-CoV-2 on people with CF is not yet known.

In conclusion, consistent with our earlier report, the outcome of SARS-CoV-2 infection for most people with CF may be less severe than originally feared. However, in this larger international cohort, it is clear that SARS-CoV-2 can result in serious consequences for some people with CF. The outcomes in this cohort may be better than the outcomes in other chronic conditions due to a possible protective effect of the relatively young median age of CF populations, lower prevalence of obesity, or other factors [8].

Table 3
Outcomes and characteristics for people with CF diagnosed with SARS-CoV-2 before 13th June 2020, who have had an organ transplant ($N = 32$).

	Hospitalisation			**Supplemental O2**			**ICU**		
	Total non-missing	**No**	**Yes**	**Total non-missing**	**No**	**Yes**	**Total non-missing**	**No**	**Yes**
	$N = 27$	$N = 7$	$N = 20$	$N = 23$	$N = 11$	$N = 12$	$N = 28$	$N = 21$	$N = 7$
Female; n (%[1])	9	4 (44)	5 (56)	8	4 (50)	4 (50)	11	11 (100)	0 (0)
Male; n (%[1])	18	3 (17)	15 (83)	15	7 (47)	8 (53)	17	10 (59)	7 (41)
Age; median (range)	38 (9–50)	38 (9–50)	38 (15–48)	39 (9–50)	40 (15–50)	38 (9–47)	38 (9–50)	38 (9–50)	38 (27–47)
Age; n (%[1])									
<18	2	1 (50)	1 (50)	2	1 (50)	1 (50)	2	2 (100)	0 (0)
18–39	14	3 (21)	11 (79)	10	4 (40)	6 (60)	14	10 (71)	4 (29)
≥40	11	3 (27)	8 (73)	11	6 (55)	5 (45)	12	9 (75)	3 (25)
Genotype; n (%[1])									
Homozygous F508del	16	4 (25)	12 (75)	13	8 (62)	5 (38)	16	13 (81)	3 (19)
Heterozygous F508del	8	2 (25)	6 (75)	7	2 (29)	5 (71)	9	6 (67)	3 (33)
Other	2	0 (0)	2 (100)	2	1 (50)	1 (50)	2	1 (50)	1 (50)
CFRD[2]; n (%[1])									
No	7	2 (29)	5 (71)	7	5 (71)	2 (29)	7	6 (86)	1 (14)
Yes	19	4 (21)	15 (79)	16	6 (38)	10 (63)	17	11 (65)	6 (35)
Pseudomonas[2]; n (%[1])									
No	9	1 (11)	8 (89)	9	4 (44)	5 (56)	12	8 (67)	4 (33)
Yes	14	4 (29)	10 (71)	13	7 (54)	6 (46)	15	13 (87)	2 (13)
Best FEV_1; median (range)	79.5 (19–114)	78 (50–99)	81 (19–114)	81 (49–114)	85 (50–99)	75.5 (49–114)	80.5 (49–114)	81 (49–114)	70 (50–91)
Best FEV_1[2]; n (%[1])									
<40	1	0 (0)	1 (100)	0	0 (0)	0 (0)	0	0 (0)	0 (0)
40–70	7	1 (14)	6 (86)	7	2 (29)	5 (71)	8	5 (63)	3 (38)
>70	12	4 (33)	8 (67)	12	7 (58)	5 (42)	16	14 (88)	2 (13)
BMI; median (range)	21 (16–29)	21 (19–25)	21 (16–29)	21 (16–29)	20 (16–25)	22 (18–29)	21 (16–29)	21 (16–29)	21 (16–24)

[1] *Row proportions are calculated from the total non-missing in each outcome.*
[2] *Where the values in a descriptive category do not add up to the overall column total (CFRD, Pseudomonas, Best* FEV_1*) this indicates incomplete data in the given descriptive.*

As of mid-August 2020, with lockdowns easing in many countries, 334 cases were known to the Global Harmonisation Group from 19 countries. The European Cystic Fibrosis Society Patient Registry (ECFSPR) reported 150 cases from 37 countries across Europe (including some participating in the Harmonization Group) on 29 July 2020 (ecfs.eu/covid-cf-project-europe). We will continue to monitor SARS-CoV-2 in people with CF and seek to report on medium and long-term outcomes, such as lung function trajectory following SARS-CoV-2 infection.

Declaration of Competing Interest

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

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2020.10.003.

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