Original Article

Clinical outcomes of adults and children with cystic fibrosis during the COVID-19 pandemic

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ABSTRACT

Background: The onset of the COVID-19 pandemic was associated with restricted community movement and limited access to healthcare facilities, resulting in changed clinical service delivery to people with cystic fibrosis (CF). This study aimed to determine clinical outcomes of Australian adults and children with CF in the 12-months following the onset of the COVID-19 pandemic.

Methods: This longitudinal cohort study used national registry data. Primary outcomes were 12-month change in percent predicted forced expiratory volume in one second (FEV1 %pred), body mass index (BMI) in adults and BMI z-scores in children. A piecewise linear mixed-effects model was used to determine trends in outcomes before and after pandemic onset.

Results: Data were available for 3662 individuals (median age 19.6 years, range 0-82). When trends in outcomes before and after pandemic onset were compared; FEV1 %pred went from a mean annual decline of -0.13% (95%CI -0.36 to 0.11) to a mean improvement of 1.76% (95%CI 1.46-2.05). Annual trend in BMI improved from 0.03 kg/m^2 (95%CI -0.02-0.08) to 0.30 kg/m^2 (95%CI 0.25-0.45) and BMI z-scores improved from 0.05 (95%CI 0.03-0.07) to 0.12 (95%CI 0.09-0.14). Number of hospitalisations decreased from a total of 2656 to 1957 ($p < 0.01$). Virtual consultations increased from 8% to 47% and average number of consultations per patient increased from median (IQR) of 4(2-5) to 5(3-6) ($p < 0.01$).

Conclusion: In the 12-months following the onset of the COVID-19 pandemic, there was an improvement in the clinical outcomes of people with CF when compared to the pre-pandemic period.

1. Introduction

Cystic fibrosis (CF) is a progressive, multi-system disease that requires lifetime treatment incorporating both inpatient and outpatient monitoring and intervention managed by CF specialist teams. The recommended frequency of clinical reviews ranges from once per month to once every three months, depending on factors such as age and the clinical condition of the patient [1]. Traditionally, reviews are conducted as face to face visits at a cystic fibrosis specialist centre (CFSC) with shared care arrangements or outreach

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clinics available for people living in remote areas. An alternative model of care is telehealth, which is the use of information and communication technologies for the purpose of providing healthcare.

Telehealth offers potential benefits such as improved access to specialty care, earlier detection of clinical changes and a reduced risk of cross-infection [2]. An additional benefit of telehealth in CF is a potential reduction in treatment burden through reducing visits to the CFSC [3]. However, there are concerns from CF clinicians about widespread use of telehealth, including ability to complete comprehensive patient assessment and ensuring equitable access [4].

In Australia, approximately 30% of people live outside of major cities [5]. As such, prior to the COVID-19 pandemic, telehealth had been investigated as an option for replacement of face-to-face clinical reviews for people living in remote locations; this model of care demonstrated improved access and high patient satisfaction [6]. The pandemic in 2020 led to a necessary and rapid increased utilisation of telehealth as a replacement of CFSC visits [7]. Early evidence from single-centre studies indicates that people with CF experience high levels of satisfaction, as well as stability in lung function and a reduction in pulmonary exacerbations [8,9].

The increased utilisation of telehealth coincided with reduced movement and interaction between people during the COVID-19 pandemic due to government-imposed movement and travel restrictions, advice against large gatherings, mandates on mask wearing and minimising social contacts to reduce virus spread [10]. Differing models of care and major changes in community interactions both have the potential to influence clinical outcomes in chronic disease. The impact on clinical outcomes of people with CF at a national level following the onset of the pandemic has not yet been reported.

The aim of this study was to assess the 12-month clinical outcomes of people with CF in Australia during the COVID-19 pandemic and associated increased utilisation of telehealth.

2. Materials and methods

2.1. Design and data source

This longitudinal retrospective cohort study used prospectively collected, de-identified patient-level data, obtained from the Australian Cystic Fibrosis Data Registry (ACFDR). The ACFDR is a central national database, comprising of outcome data on an estimated 95% of adults and children with CF in Australia [11]. Data are entered following each encounter for individual patients by trained staff at all Australian CFSCs, with data entry due on a quarterly basis. Ethical approval was obtained through the Sydney Children's Hospitals Network Human Research Ethics Committee (2020/ETH03137).

Data were obtained for time periods before and after the onset of the COVID-19 pandemic in Australia. The 16th March 2020 was chosen as the date from which impacts of the pandemic would be assessed (index date). The index date represents the time at which the Australian government restricted numbers allowed to gather publicly and is also commencement of the first week in which funding was approved for outpatient reviews to be conducted by telehealth for all patients to assist in limiting attendance at health facilities [12]. Prior to the index date, telehealth was only funded for patients living >100km from a major city. Telehealth appointments were entered into the ACFDR as either videocall or telephone only appointments.

2.2. Study population

Adults and children who had consented to having their data included in the ACFDR and attended a CF specialist centre through-out the data review period were included. Children less than 2 years of age on the index date were excluded from the analysis of nutritional outcomes as the gold standard method of reporting nutritional outcomes changes from weight for length z-score to BMI z-score at 2 years of age. Therefore, longitudinal nutritional outcome data would not be possible for children who turned 2 during the study period. In addition, patients who underwent transplant in the study period were excluded from the analysis.

2.3. Clinical outcomes

For the primary outcome measures, the period for 24-months prior to index date was used to establish the baseline trends for comparison to the period following pandemic onset. Primary outcomes were trends in percent predicted Forced Expiratory Volume in one second (FEV1 %pred), BMI z-score or raw BMI depending on patient age. FEV1 %pred was calculated based on the Global Lung Initiative (GLI) reference equations.

The ACFDR records BMI z-score up until age 20 and BMI for all ages. Therefore, to allow for a consistent longitudinal outcome measure for the entire data review period, BMI z-score was adopted for participants aged ≤17 years and raw BMI was adopted for participants >17 years of age at the commencement of the data collection period.

Secondary outcomes included number of hospitalisations for CF related issues, duration and delivery location of intravenous antibiotics (IVAB), and number and location of outpatient clinical reviews. For secondary outcome measures, the period for 12-months prior to and 12-months following pandemic onset were used to allow direct comparison.

2.4. Statistical analysis

For the primary outcome measures, longitudinal trends in FEV1 %pred, BMI and BMI z-scores over the data review period were calculated. To determine trends before and after pandemic onset, a piecewise linear mixed-effects model was developed. Time was included in the model, with the index date being 16/3/2020. The piecewise analysis was used to determine the slope of the line in the 24 months prior to and the 12 months following the index date. In addition, random effects for patient and clinic were added to the model to account for the non-independence of repeat measures on patients and to account for groups of patients having their care managed at specific CFSCs. A linear combination of coefficients was used to test for statistical significance in slopes before and after the index date. An additional analysis comparing trends in the 12 months before and after the index date was also conducted.

The piecewise linear mixed-effects model was extended to include known potential confounders of clinical outcomes in individuals with CF. The variables included in the multivariable model were: gender, age, *P. aeruginosa* status and CF modulator therapy use. *P. aeruginosa* status was based on the presence of *P. aeruginosa* on any sample within each time period, with participants classified as having *P. aeruginosa* present (yes/no) in each period. If no bacterial culture results were entered into the ACFDR during the study period, unknown *P. aeruginosa* status was assigned to the individual. Additionally, the analysis for FEV1 %pred was stratified by age group.

For the secondary outcome measures; a McNemar's test was used to compare hospitalisation data and clinic visit type for the time periods before and after pandemic onset. A Wilcoxon signed-rank test was used to compare average number of clinic visits and number of clinical measures obtained per person in the 12-months before and after the index date. Significance level was set at 0.05.

Table 1

Demographics and characteristics of participants at commencement of the data collection period for primary outcome measure (16/3/2018).

Age, mean (SD)	20.2 (14.8)
Age range, n(%)	
<6 years	652 (18)
6 to 11 years	609 (17)
12 to 17 years	559 (15)
≥ 18 years	1842 (50)
Gender, M/F, n(%)	1930/1732 (52%/48%)
P. aeruginosa present y/n/unknown	1117/1691/854
FEV1 % predicted entire cohort, mean (SD)	73.9 (24.1)
5-12 years	92.2 (15.3)
12 to 17 years	81.7 (18.4)
≥ 18 years	66.1 (24.4)
BMI kg/m^2 (participants aged ≥ 17 years), mean (SD)	20.1 (4.3)
BMI z-score (participants aged 2 to <17 yrs), mean (SD)	-0.04 (0.97)
Highly effective modulator use, n (%)	
Ivacaftor	261 (7.1%)
Elexacaftor/Tezacaftor/Ivacaftor	15 (0.4%)
Other modulator use	
Lumacaftor/Ivacaftor	771 (21%)
Tezacaftor/Ivacaftor	129 (3.5%)

FEV1, forced expiratory volume in one second; BMI, body mass index

Table 2

Baseline values and multivariable-adjusted slope* in Forced Expiratory Volume in one-second percent predicted (FEV1 %pred) in the 24 months before the index date and the 12 months following the index date. *p* value tests whether the slope is significantly different to zero for that time period.

	Mean	95% CI	*p* value
Entire Cohort (n=3112)			
FEV1 %pred at study entry (SD)	73.9 (24.1)		
Annual slope before index date	-0.13	-0.36 to 0.11	0.284
Annual slope after index date	1.76	1.46 to 2.05	<0.001
Change in slope before vs after	1.89	1.58 to 2.20	<0.001
Age 5- 12 years			
FEV1 %pred at study entry (SD)	92.2 (15.3)		
Annual slope before index date	-0.46	-1.16 to 0.24	0.201
Annual slope after index date	0.97	0.09 to 1.85	0.030
Change in slope before vs after	1.43	0.54 to 2.31	<0.001
Age 12 to 17 years			
FEV1 %pred at study entry (SD)	81.7 (18.4)		
Annual slope before index date	0.99	0.35 to 1.64	<0.001
Annual slope after index date	3.78	3.07 to 4.50	<0.001
Change in slope before vs after	2.79	2.14 to 3.43	<0.001
Age ≥ 18 years			
FEV1 %pred at study entry (SD)	66.1 (24.4)		
Annual slope before index date	-0.38	-0.69 to -0.08	0.011
Annual slope after index date	1.29	0.90 to 1.69	<0.001
Change in slope before vs after	1.68	1.28 to 2.08	<0.001

* Adjusted for age, sex, modulator use and *P. aeruginosa* presence

3. Results

3.1. Study population and data completeness

Data were available for 3662 individual people with CF (1930 males, 1732 females, median age 19.6 years, range 0-82) (Table 1). Overall data completeness was >95% for primary and secondary outcome measures during the data collection period (Supplemental Table S1).

3.2. Clinical outcomes

The observed trend in FEV1 %pred improved after the index date in the entire cohort, as well as in each age group (Table 2). In the 5-12-year age group and the ≥18 age group, there was a decline in FEV1 %pred trends in the 24 months prior to the index date, whereas in the 12 months following the index date there was

Table 3

Baseline values and slope in body mass index (BMI) and BMI z-score in the 24 months before the index date and the 12 months following the index date. p value indicates if the slope is significantly different to zero for that time period.

Effect	Mean	95% CI	*p* value
Age ≥17 years at index date (n=1684)			
BMI kg/m^2 at study entry (SD)	20.1 (4.3)		
Annual slope before index	0.03	-0.02 to 0.08	0.223
Annual slope after index	0.30	0.25 to 0.35	<0.001
Change in slope before vs after	0.27	0.23 to 0.31	<0.001
Age 2 to <17 years at index date (n=1978)			
BMI z-score at study entry (SD)	-0.04 (0.97)		
Annual slope before index	0.05	0.03 to 0.07	<0.001
Annual slope after index	0.12	0.09 to 0.14	<0.001
Change in slope before vs after	0.07	0.04 to 0.09	<0.001

Table 4

Hospitalisations in the 12-month period pre and post the index date, reported as total number of events with number of individuals in (). IVAB; Intravenous antibiotics.

	Pre-Index	Post-Index	*p* value
Total hospitalisations	2656 (1338)	1957 (1108)	<0.001
Gastrointestinal or respiratory hospitalisations	2359 (1292)	1677 (998)	<0.001
Courses of IVAB	2115 (1196)	1569 (970)	<0.001
Hospital only IVAB courses	1589 (920)	1075 (670)	<0.001
IVAB fully/partially at home	526 (389)	494 (391)	0.9016
Duration of IVAB, median (IQR)	13 (9-15)	13 (9-14)	0.1013

an improvement. In the 12-to-17-year age group, the slope in the 24 months before the index date was positive and became more positive in the 12 months following the index date. When analysis was performed comparing the 12 months before and after the index date, there was also a significant improvement in the observed trend in FEV1%pred following the index date (Supplemental Table S2). Multivariate adjusted model predicted slopes and intercepts of FEV1 %pred corresponding to raw FEV1 %pred values in Table 2 are presented in Supplemental Figure SF1.

BMI before the pandemic onset was stable, followed by a small, statistically significant upward trend in the 12 months following the index date. In the paediatric cohort, the trend in BMI z-score improved before the index date, and significantly more so after the index date (Table 3).

3.3. Hospitalisations and use of IVAB

There was a statistically significant reduction in the number of people with CF being hospitalised in the 12 months following the index date compared to the 12 months prior ($p < 0.001$). There was a 26% reduction in courses of IVAB administered in the post-index period. The observed reduction was mainly seen in hospital administered courses of IVAB, with a relatively small decrease in home administered IVAB (Table 4).

3.4. Outpatient clinical reviews

In the pre-index period, 92% of outpatient clinical reviews were conducted face to face and 8% were conducted virtually via telehealth with videocall or telephone only. In the post-index period, 53% of outpatient clinical reviews were conducted face to face and 47% were conducted virtually (Table 5). In the post-index period, there was an increase in total number of outpatient clinical reviews as well as an increase in average outpatient reviews per person from a median (IQR) of 4 [2–5] to 5 [3–6] per individual ($p < 0.001$) (Table 5). Despite an overall increase in number of outpatient reviews, there was a reduction in the number of clin-

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Table 5

Outpatient clinical reviews by type in the 12-month period pre and post the index date

	Pre	Post	*p* value
Consultations per person, median (IQR)	4 (2-5)	5 (3-6)	<0.001
Face to face clinical reviews (n)			
At CF Specialist Centre	11425	8490	
At outreach clinic	363	675	
Total	11788	9165	<0.001
Virtual clinical reviews (n)			
Videocall appointments	975	6222	
Telephone appointments	40	2036	
Total	1015	8258	<0.001
Proportion of total clinical reviews conducted virtually (%)	7.9%	47.4%	<0.001

ical measures entered into the ACFDR in the 12 months post the index date (Supplementary Table S3).

4. Discussion

This study has demonstrated that the COVID-19 pandemic forced a change in the CF model of clinical care delivery. Clinical outcomes, including lung function, BMI and hospitalisations for CF related issues were improved in the 12 months following the onset of the pandemic. Use of longitudinal national registry data which includes data for an estimated 95% of Australian adults and children with CF, with a data entry completion rate of >95% for key clinical outcome measures in the study period supports the validity of these findings.

A main finding from this study was the improvement in lung function in the 12 months post pandemic onset. Recent European studies comparing clinical outcomes in adults and children with CF also show an improvement in lung function following an initial 2-3 month pandemic driven lockdown period [13,14]. However, these studies have been limited by comparison of only a single lung function value before and after a short lockdown period and data were only collected at single centres, whereas the current study has the advantage of using longitudinal national data. In the 2 year period prior to the pandemic, there was a small decline in FEV1 %pred of -0.13% per annum which was not statistically different from zero. The finding of almost stable lung function in the pre-index period within this study is different from the decline which has previously been reported in longitudinal studies of lung function in individuals with CF [15].

In methodology more similar to the current study, Somerville et al. [8] looked at 12-month change in FEV1 %pred following pandemic onset in a single North American CFSC. Whilst the authors reported an improved FEV1 %pred, the improvement became non-significant when the effect of highly effective CFTR modulators was accounted for. In the current study, the use of highly effective CFTR modulator therapies were only available to a small percentage of the CF population. During the study period, the only government funded highly effective modulator therapy that was widely available was ivacaftor for people with a G551D or other CFTR gating mutation, which accounted for approximately 7% of the Australian CF population. The other highly effective modulator therapy, Elezacaftor/tezacaftor/ivacaftor, was not government funded and only available through clinical trials or a compassionate access scheme.

At the commencement of the pre-index period, approximately 15 individuals were recorded as receiving Elezacaftor/tezacaftor/ivacaftor. This figure increased to 240 by the end of the study period. A strength of this study is that even though there was not widespread use of highly effective modulators in the Australian CF cohort, commencing any modulator therapy was included in the statistical model as a potential con-

founder and found not to impact the overall findings. Therefore, the improved trend in FEV1 %pred in the post-index period could not be attributed to the use of modulator therapies. To confirm the robustness of the primary finding of an improved FEV1 post onset of the pandemic, a sensitivity analysis was undertaken in which participants who had received modulator therapy were excluded from the analysis. The removal of these participants did not impact the findings (Supplemental Table S4).

The current study showed a reduction in use of IVAB following pandemic onset. Pulmonary exacerbations are known to be associated with a more rapid decline in FEV1 %pred in people with CF [16], therefore, a reduction in exacerbations in the post-index time period may have contributed to the improved trend in FEV1 %pred. Given the source of data was the ACFDR, options for recording a more standardised definition of an exacerbation based on clinical criteria was not possible, therefore, number of exacerbations may have been underestimated in the post-index period. However, using a wider definition of pulmonary exacerbations including illnesses requiring either oral or IV antibiotics, multiple studies have also reported a reduction in exacerbations after the pandemic onset [8,9], indicating a true reduction in pulmonary excaerbations.

The finding of reduced respiratory exacerbations during the pandemic is not unique to CF. A recent systematic review and meta-analysis reported a 50% reduction in hospitalisations due to respiratory exacerbations in people with chronic obstructive pulmonary disease during the pandemic [17]. In children with asthma, there has also been an observed reduction in upper respiratory tract infections, presentations to emergency departments and hospitalisations [18].

A potential explanation for a reduction in pulmonary exacerbations shown in people with CF and other respiratory diseases is the reduction in exposure to respiratory viruses, not just SARS-CoV2, during the period of pandemic restrictions. Following pandemic onset, there was a drastic reduction in detection of respiratory viruses such as rhinovirus, RSV and influenza in Australia [19]. There is a known association between respiratory viruses and pulmonary exacerbations in CF [20]. Therefore, whilst presence of respiratory viruses was not directly measured in the study cohort, reduced circulating virus activity may have contributed to the observed reduction in exacerbations.

In addition to an improved trend in lung function, there was also a small, statistically significant observed improvement in BMI of 0.27kg/m^2 in the adult group and BMI z-score of 0.07 in children. Whilst the clinical significance of small improvements is unkown, cumulative improvements if they were to continue would be of greater clinical significance. Somerville et al. [8] also reported increased BMI in adults with CF in the period following pandemic onset, however, approximately 85% of the participants in that study commenced highly effective CFTR modulator therapies and the effect of commencing modulators was unable to be included in their analysis of BMI.

There are multiple potential reasons for the increase in BMI and BMI z-score seen in this study. Pulmonary exacerbations are associated with increased energy expenditure [21], therefore, reduced incidence of pulmonary exacerbations in the post-index period may have positively influenced BMI. Another potential explanation for increased BMI is reduced levels of physical activity during the pandemic [22] and other pandemic related behaviours such as increased snacking on energy dense foods [23]. An alternative measure such as fat free mass index would be helpful in elucidating the impact of the pandemic on nutritional status, however, fat free mass index is not a routinely collected clinical measure.

An additional finding in the current study which may have contributed to improved clinical outcomes was the overall significant increase in number of clinical reviews undertaken. The increased utilisation of telehealth resulted in an average annual increase of

approximately one review per person. Despite the increase in number of reviews, fewer clinical measures were recorded, likely due to less availability and/or consistency of measurements being taken in the home environment. Internationally, there has also been a trend to an overall increased number of clinical reviews following the onset of the COVID pandemic [7,24], indicating that despite limitations to the traditional model of face to face care, the adapted model of CF clinical care delivery resulted in more outpatient reviews.

There are a number of limitations in this study. The main limitation is that due to the retrospective design of the study, no conclusions are able to be drawn regarding the cause of the improved clinical outcomes observed during the COVID-19 pandemic. Multiple factors, including reduced commnity interaction and reduced exposure to respiratory viruses, as well as a change to a more remote model of care may have contributed to the findings. However, without a prospective study design and allocation to different conditions, causation is unable to be determined.

Another limitation of this study is the lack of standardisation in the way that clinical measurements, such as spirometry and height/weight measures, were taken in the pre and post index periods. With the increased number of virtual reviews in the post index period, less hospital-based measurements and more home-based measurements were likely to be entered into the database, leading to the potential of inaccuracies in the measurements taken. For example, in the paediatric cohort, if a previous height and not an updated height was used to calculate FEV1 %pred, a falsely elevated finding may be reported [25]. Given that the increase in FEV1 %pred was also present in adults, where height is more stable, any impact of inaccurate height measurements in the paediatric cohort seems unlikely to have led to the reported improvement in lung function. An additional limitation was in regard to classification of *P. aeruginosa* presence. The recommended definition of ≥50% of samples being positive for *P. aeruginosa* for a patient to be classified as having chronic *P. aeruginosa* infection was unable to be applied, as this classification is recommended to be based on a minimum of 6 samples per year [26]. The median number of sample results entered into the database in the pre and post index years were 1 and 2 respectively (Supplemental Table S3). Therefore, the authors proceeded with the approach of classifying *P. aeruginosa* as being present or not based on a positive *P. aeruginosa* result on any sample within each time period.

This study has shown a major shift in the model of care delivered to people with CF to incorporate more virtual appointments during the COVID-19 pandemic. This change in model of care, without prospective evaluation, poses challenges to deciding on how best to deliver care following the COVID-19 pandemic. It is likely that increased use of telehealth will persist, as advantages such as reduced treatment burden, increased access to care and reduced risk of cross-infection have been reported [27]. However, potential risks and barriers to telehealth, such as access to technology, difficulties with performing assessments such as spirometry, microbiological monitoting and mental health screening have also been identified [28, 29]. In addition, and importantly, the barriers are most evident in racial/ethnic minority populations and those with financial difficulties, resulting in reduced use of telehealth in these groups during the pandemic [30]. Therefore, whilst the results of this study are promising, the future model of care, once pandemic related factors such as government restrictions and increased availability of funding for telehealth are no longer present, requires careful consideration.

In the 12 months following the onset of the COVID-19 pandemic, restrictions on movement of people led to reduced community interaction, reduced circulating respiratory viruses and a change in model of care to incorporate more remote consultations. This national study, comprising of data on approximately 95% of the Australian adult and paediatric CF population showed an associated improvement in clinical outcomes and a reduction in exacerbations in Australians with CF.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2022.09.006.

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